Filed Pursuant to Rule 424(b)(3)
Registration No. 333-230944

11,547,058 Shares

Common Stock

This prospectus relates to the resale of an aggregate of 11,547,058 shares of our common stock, by the selling stockholders identified in this prospectus who acquired the securities in a private placement pursuant to that amended and restated common stock purchase agreement, dated as of February 25, 2019, by and among us and the selling stockholders listed therein, or the purchase agreement.

We are registering the offer and sale of the shares by the selling stockholders to satisfy certain registration rights we have granted to the selling stockholders. We are not selling any shares under this prospectus, and we will not receive any of the proceeds from the sale of the shares by any of the selling stockholders. See "Use of Proceeds." We will pay for any expenses incurred incident to registering the shares.

The selling stockholders may sell the shares described in the prospectus in a number of different ways and at varying prices. We provide more information about how the selling stockholders may sell their shares in the section of this prospectus titled "Plan of Distribution."

The selling stockholders may sell any, all or none of the shares and we do not know when or in what amounts the selling stockholders may sell their shares hereunder following the effective date of this registration statement.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "CYCN." On April 17, 2019, the last reported sale price for our common stock as reported on Nasdaq was $16.23 per share.

We are an "emerging growth company" as defined under the federal securities laws, and as such, we have elected to comply with certain reduced reporting requirements for this prospectus and may elect to do so in future filings. See the section titled "Prospectus Summary—Implications of Being an Emerging Growth Company."

See "*Risk Factors*" beginning on page 10 to read about the factors you should consider before buying shares of our common stock and any risk factors described in any accompanying prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission or other regulatory body has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

Prospectus dated April 23, 2019

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Neither we nor the selling stockholders have authorized anyone to provide you with any information or to make any representations other than those contained in this prospectus, any prospectus supplement or in any free writing prospectuses we have prepared. We and the selling stockholders take no responsibility for, and provide no assurance about the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of our common stock. Our business, financial condition, results of operations, and prospects may have changed since such date.

For investors outside the United States: Neither we nor the selling stockholders have done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. You are required to inform yourselves about, and to observe any restrictions relating to, this offering and the distribution of this prospectus.

PROSPECTUS SUMMARY

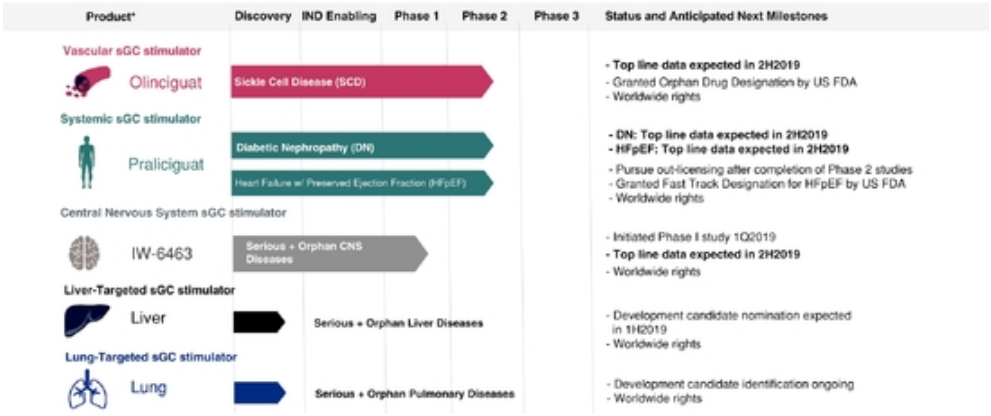
This summary highlights information appearing elsewhere in this prospectus. This summary does not contain all the information you should consider before investing in our common stock. You should read this entire prospectus carefully, including the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes included elsewhere in this prospectus, before making any investment decision. Unless the context otherwise requires, we use the terms "Cyclerion," the "company," "we," "us," and "our" in this prospectus to refer to Cyclerion Therapeutics, Inc. and, where appropriate, our consolidated subsidiaries.

Our Business

Overview

We are a clinical-stage biopharmaceutical company harnessing the power of soluble guanylate cyclase, or sGC, pharmacology to discover, develop and commercialize breakthrough treatments for serious and orphan diseases. Our focus is enabling the full therapeutic potential of next-generation sGC stimulators. sGC stimulators are small molecules that act synergistically with nitric oxide on sGC to boost production of cyclic guanosine monophosphate, or cGMP. cGMP is a key second messenger that, when produced by sGC, regulates diverse and critical biological functions throughout the body including blood flow and vascular dynamics, inflammatory and fibrotic processes, metabolism and neuronal function. We believe that the key to unlocking the full therapeutic potential of the nitric oxide-cGMP pathway is to design differentiated next-generation sGC stimulators that preferentially modulate pathway signaling in tissues of greatest relevance to the diseases they are developed to treat. This targeted approach is intended to maximize the potential benefits of nitric oxide-cGMP pathway stimulation in disease-relevant tissues. We are led by an accomplished team, many of whom have worked together previously at Ironwood Pharmaceutics, Inc., or Ironwood, with an exceptional track record of discovering, developing and commercializing meaningful therapies for patients while creating value for stockholders. Our strategy rests on a solid scientific foundation that is enabled by our people and capabilities, external collaborations and a responsive capital allocation approach.

We have an extensive portfolio of five differentiated sGC stimulator programs with several pipeline catalysts expected in 2019. The following table summarizes our programs:



Status of selected key development programs as of April 8, 2019. Represents current phase of development, does not correspond to the completion of a particular phase.

Strategic Core

We leverage the therapeutic potential of nitric oxide signaling by modulating the nitric oxide-cGMP pathway via pharmacologically tailored sGC stimulation. Nitric oxide signaling plays a central role in regulating diverse aspects of human physiology throughout the body, including vascular smooth muscle tone and blood flow, as well as processes that influence inflammation, fibrosis, metabolism and neuronal function. Deficient nitric oxide signaling is linked to a wide range of cardiovascular, metabolic, inflammatory, fibrotic and neurological diseases. Stimulation of sGC is clinically validated by ADEMPAS®, an sGC stimulator marketed by Bayer AG, or Bayer, that represents an important first step in demonstrating the therapeutic potential of this mechanism. In order to realize the significant potential of sGC stimulation to enable the development of important new medicines, we are focused on developing next generation sGC stimulators.

We design sGC stimulators with distinct pharmacologic and biodistribution properties that preferentially enhance nitric oxide-cGMP signaling in target tissues of greatest relevance to the diseases they are developed to treat. The resulting sGC stimulators are highly differentiated from each other, as well as from other sGC modulators and molecules that target this pathway via other mechanisms. This approach to the therapeutic application of nitric oxide-cGMP pharmacology is intended to allow us to harness the powerful multidimensional pharmacology of sGC stimulation for clinical application in serious and orphan diseases.

We have discovered and are advancing a pipeline of five differentiated sGC stimulator programs whose properties are tailored for distinct serious and orphan diseases with significant unmet clinical need.

- ***Olinciguat is an orally administered, once-daily, vascular sGC stimulator*** that we believe is well suited for the treatment of sickle cell disease, or SCD, given its distribution to the vasculature and highly perfused organs, such as the kidney and lungs, which are frequently affected by this disease. By amplifying nitric oxide signaling, we believe that olinciguat has the potential to reduce the proportion of sickled cells, decrease vascular inflammation and cell adhesion, and improve nitric oxide-mediated vasodilation. For patients with SCD, we believe this may translate into reduction in debilitating daily symptoms such as chronic pain and fatigue, decrease in anemia, reduction in painful vaso-occlusive crises, or VOCs, and end-organ protection (especially for the kidney, heart and lung) potentially leading to an increase in survival. Olinciguat has been granted Orphan Drug Designation for SCD by the U.S. Food and Drug Administration, or the FDA, and is currently in a Phase 2 study, STRONG-SCD, that is expected to enroll approximately 88 patients. Following the completion of our ongoing Phase 2 study, should data warrant, we intend to advance olinciguat into late-stage development for SCD and, if approved, commercialize on our own in the United States and alone or through licensing arrangements with partners around the world. We expect results from this study in the second half of 2019.

- ***Praliciguat is an orally administered, once-daily systemic sGC stimulator*** that we believe is well suited for the treatment of serious cardiometabolic diseases given its very extensive distribution into tissues, particularly adipose, kidney, heart and liver. We believe this distribution profile is essential to realize the potential of sGC pathway pharmacology to treat cardiometabolic diseases that are characterized by adipose inflammation, metabolic dysfunction and associated multi-organ etiology and involvement. We are assessing the potential of praliciguat to treat two such diseases: diabetic nephropathy, or DN, and heart failure with preserved ejection fraction, or HFpEF. We expect results from Phase 2 studies in these indications in the second half of 2019.

- ***IW-6463 is an orally administered CNS-penetrant sGC stimulator*** that, because it readily crosses the blood-brain barrier, affords an unprecedented opportunity to expand the utility of sGC pharmacology to serious neurodegenerative diseases. Clinical and nonclinical research suggests that nitric oxide signaling plays a critical role in the central nervous system, or CNS, in memory

formation and retention, control of cerebral blood flow and modulation of neuroinflammation. Nitric oxide is a potent neurotransmitter, and impaired nitric oxide-sGC-cGMP signaling is believed to play an important role in the pathogenesis of several neurodegenerative diseases. In preclinical models, IW-6463 has been associated with an increase in cerebral blood flow, improved neuronal health and function, reduced markers of neuroinflammation and enhanced cognition. CNS pharmacological activity of IW-6463 has been observed preclinically using multiple non-invasive techniques that can also be employed in early human clinical studies. Our first-in-human study of IW-6463 initiated in January of 2019 with results expected in the second half of 2019.

- ***Our liver-targeted sGC stimulator*** will be orally administered and designed to selectively partition to the liver. By achieving liver concentrations many fold higher than corresponding plasma concentrations, we intend to maximize hepatic pharmacology. In animal models of liver fibrosis treated with systemic sGC stimulators, we have observed reductions in liver fibrosis, inflammation and steatosis, pathophysiological processes that underlie multiple chronic liver diseases. We expect to nominate a development candidate in the second quarter of 2019 and progress to filing an Investigational New Drug/Clinical Trial Application, or IND/CTA, thereafter.

- ***Our lung-targeted sGC stimulator*** will be administered via inhalation and will be aimed at realizing the full potential of sGC stimulation in pulmonary diseases by selectively increasing exposure in the lung. Preclinically, our lead molecule is highly retained in the lung with greater than 50-fold selectivity for lung over plasma. In addition, in preclinical studies, the lead molecule is metabolically stable in the lung, whereas it is unstable in the plasma with rapid systemic clearance. We are pursuing the identification of a development candidate, and expect to progress to filing an IND/CTA, thereafter.

We have a comprehensive intellectual property strategy to protect our platform and related proprietary technology that covers composition of matter, method of use, formulations and process development.

Value-Creating Enablers

People and capabilities

We are leaders in targeted sGC stimulator chemistry and nitric oxide-cGMP pathway pharmacology. Our founding team has deep knowledge and significant experience in cGMP pathway research and development, from the discovery and development of LINZESS® (linaclotide), an Ironwood product that leverages the pharmacology of the guanylate cyclase-C-cGMP pathway, to the development of the sGC stimulator chemistry libraries and systems pharmacology data that gave rise to the current portfolio of assets and will serve as the foundation for our future innovation.

We have an exceptional team with a proven track record at all levels within our organization. We have broad expertise throughout our organization in discovering, developing and commercializing category-leading products, and are led by a management team with a history of success delivering innovative therapies to patients while creating value for stockholders.

External collaboration

We leverage a diverse cross-disciplinary network of external advisors and experts to advance our drug candidates. We do this in three ways. First, we actively engage leading experts to access additional technologies and expertise to advance our programs. Second, we establish disease-area advisory boards of physicians, patients and payors to provide insights into the unmet medical need and to support the design of clinical trials. Finally, we use a pharmaceutical advisory board made up of veteran drug

hunters with broad industry experience and a track record of innovation to help us refine our R&D strategy.

We will apply a "best-owner" approach to our compounds whereby we develop and commercialize product candidates independently or through a partner depending on which path we believe will offer the greatest risk-adjusted value for our shareholders and accelerate global patient access to our drugs. We intend to prioritize development and commercialization in diseases characterized by structurally attractive markets where we can successfully commercialize on our own. At this time, we do not have any partnerships for any of our product candidates and we intend to apply this "best owner approach" as we make decisions regarding potential partnerships.

Capital allocation and economics

The capital allocation decision making and financial management we use in our business will enable us to continually deploy capital and people to the most promising opportunities. Highlights of our capital allocation and financial management strategy include:

- **Decisive capital allocation:** We plan to establish a high threshold for therapeutic differentiation and compelling business case in each program.
- **Elastic, externalized cost structure:** Our experienced team will seek to use outside supplier/partners wherever possible, in order to benefit from any economies-of-scale and skill sets that such suppliers and partners provide while minimizing our fixed costs.
- **Mission-appropriate infrastructure:** Our infrastructure is designed to meet the needs of a multi-program development company intent on prosecuting and developing the sGC mechanism, generating and protecting key intellectual property, compliance and attracting and retaining talent to further advance our five lead sGC stimulator programs and discover additional disease-targeted sGC stimulators.
- **Development program-based management structure:** Our program leaders are accountable for performance against goals for each program based on clinical and scientific, cost and timeline performance metrics.

Summary of Risk Factors

An investment in our common stock is subject to a number of risks, including risks related to our business, risks related to our separation from Ironwood, or the separation, and risks related to our common stock. The following list of risk factors is not exhaustive. Please read the information in the section captioned "Risk Factors" for a more thorough description of these and other risks.

Risks Related to Our Business

- Because we are a clinical-stage biopharmaceutical company with a limited operating history and no products approved for commercial sale, valuing our business and predicting our prospects is challenging.
- Our business has incurred significant losses and we anticipate that we will continue to incur significant losses for the foreseeable future.
- We will need to raise additional funding to advance our product candidates, which may not be available on acceptable terms, or at all.
- The "target-to-disease" approach we are taking to discover and develop product candidates targeting the cGMP may never lead to marketable products.

- We may encounter substantial delays in our clinical studies, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.
- If we encounter difficulties in enrolling subjects in our clinical studies, we could be delayed or prevented from proceeding with clinical trials of our product candidates.
- The regulatory approval processes of the FDA, and comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable.
- Our product candidates may cause undesirable side effects that delay or prevent their regulatory approval, result in label restrictions or result in harmful consequences.
- We face significant competition, including from approved products and product candidates in development, and our competitors may achieve regulatory approval before us or develop therapies that are safer, more advanced or more effective than ours.
- If third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.
- We rely completely on third-party suppliers to manufacture our clinical drug supplies for our product candidates, and we intend to rely on third parties to produce non-clinical, clinical and commercial supplies of any future product candidate.
- If we are unable to adequately protect our proprietary technology, others could compete against us more directly, which would have a material adverse impact on our business, prospects, financial condition and results of operations.
- If the market opportunities for our product candidates are smaller than we estimate, or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability may be harmed.
- Even if we obtain regulatory approval for our product candidates, our product candidates may not achieve broad market acceptance by patients, physicians, healthcare payors or others in the medical community.
- Our ability to generate meaningful revenues in foreign countries may be limited due to the strict price controls and reimbursement limitations imposed by governments outside of the United States.

Risks Related to the Separation and the Private Placement

- We may not achieve some or all of the expected benefits of the separation, and the separation could harm our business, prospects, financial condition and results of operations.
- We have no history of operating as an independent company and we expect to incur increased administrative and other costs following the separation by virtue of our status as an independent public company.
- The separation may impede our ability to attract and retain key personnel, which could materially harm our business.
- The separation may result in disruptions to, and harm our relationships with, our strategic business partners.
- If the distribution, together with certain related transactions, does not qualify as a transaction that is tax-free for U.S. federal income tax purposes, Ironwood and its stockholders could be subject to significant tax liabilities, and we could be required to indemnify Ironwood for material

taxes pursuant to indemnification obligations under a tax matters agreement we entered into with Ironwood.

- We may not be able to engage in attractive strategic or capital-raising transactions following the separation.
- Our agreements with Ironwood may not reflect terms that would have resulted from negotiations with unaffiliated third parties.

The Separation and Distribution

In May 2018, Ironwood announced its plans to separate its sGC business from its commercial and gastrointestinal business. In furtherance of this plan, on March 6, 2019, Ironwood's board of directors approved the distribution of all of the issued and outstanding shares of our common stock on the basis of one share of Cyclerion common stock for every 10 shares of Ironwood common stock issued and outstanding on March 19, 2019, the record date for the distribution. For purposes of this prospectus, the foregoing is referred to in this prospectus as the distribution. As a result of the distribution, we became an independent, publicly traded company on April 1, 2019.

On March 30, 2019 we also entered into a separation agreement with Ironwood, which is referred to in this prospectus as the separation agreement, and have since entered into various other agreements with Ironwood, including a tax matters agreement, an employee matters agreement, a development agreement, an intellectual property license agreement, a transition services agreement under which we temporarily receive certain services from Ironwood, and a second transition services agreement under which we temporarily provide certain services to Ironwood. These agreements also govern certain of our relationships with Ironwood after the separation. For additional information regarding the separation agreement and the other related agreements, see "Risk Factors—Risks Related to the Separation" and "Certain Relationships and Related Person Transactions—Agreements with Ironwood."

Corporate Information

We were incorporated in the Commonwealth of Massachusetts on September 6, 2018 for the purpose of holding Ironwood's sGC business in connection with the separation described in this prospectus. The contribution of this business to us occurred over a period of time prior to the distribution, and we had no operations prior to such contribution. Our principal executive offices are located at 301 Binney Street, Cambridge, MA 02142. Our telephone number is 857-327-8778. You can access our website at *www.cyclerion.com*. Information on, and which can be accessed through, our website is not incorporated in, and does not form a part of, this prospectus.

Implications of Being an Emerging Growth Company

We qualify as an "emerging growth company" as defined in the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other obligations that are otherwise applicable generally to public companies. These may include the following:

- being permitted to present only two years of audited financial statements (as a result of our status as a smaller reporting company), in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements;
- exemption from the requirements for holding a non-binding advisory vote on executive compensation or golden parachute arrangements;

- extended transition period for complying with new or revised accounting standards; and
- exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We may take advantage of these provisions for up to five years or such earlier time that we are no longer an emerging growth company. We will cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total gross annual revenues of $1.07 billion or more; (ii) December 31, 2024, the last day of our fiscal year following the fifth anniversary of the date of the distribution; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

THE OFFERING

Common stock offered by the selling stockholders	11,547,058 shares
Total common stock outstanding after this offering	27,401,660 shares
Use of proceeds	The selling stockholders will receive all of the net proceeds from this offering. We will not receive any proceeds from the sale of shares of common stock by the selling stockholders. See "Use of Proceeds."
Plan of Distribution	The selling stockholders may offer the shares in amounts, at prices and on terms determined by market conditions at the time of the offering. The selling stockholders may sell shares through agents they select or through underwriters and dealers they select. The selling stockholders also may sell shares directly to investors. If the selling stockholders use agents, underwriters or dealers to sell the shares, we will name them and describe their compensation in a prospectus supplement. See "Plan of Distribution."
Risk factors	You should read the "Risk Factors" section beginning on page 10 and the other information included in this prospectus for a discussion of factors to consider before deciding to invest in shares of our common stock.
Nasdaq Global Select Market ticker symbol	"CYCN"

Unless we indicate otherwise, all information in this prospectus is based on 27,401,660 shares of our common stock outstanding as of April 2, 2019, and excludes:

- 400,000 shares of common stock reserved for future issuance under our 2019 Employee Stock Purchase Plan, as of April 2, 2019;
- 2,487,895 shares of common stock reserved for future issuance under our 2019 Equity Incentive Plan, as of April 2, 2019;
- 6,456,982 shares of common stock issuable upon the exercise of stock options outstanding as of April 2, 2019; and
- 932,469 shares of common stock issuable upon the vesting and settlement of restricted stock units outstanding as of April 2, 2019.

SUMMARY HISTORICAL AND UNAUDITED PRO FORMA COMBINED FINANCIAL INFORMATION

The following table presents our summary historical and unaudited pro forma combined financial information. We derived the summary historical combined financial data as of and for the years ended December 31, 2017 and 2018 from our audited combined financial statements included elsewhere in this prospectus.

The summary historical combined financial data includes certain expenses of Ironwood that were allocated to us for certain corporate functions including information technology, research and development, finance, legal, insurance, compliance and human resources activities. These costs may not be representative of the future costs we will incur as an independent, publicly traded company. In addition, our historical financial information does not reflect changes that we expect to experience in the future as a result of our separation from Ironwood, including changes in our cost structure, personnel needs, tax structure, capital structure, financing and business operations. The following summary unaudited pro forma combined financial information gives effect to the separation and the private placement, as if each had occurred on January 1, 2018. The unaudited pro forma adjustments are based on assumptions that our management believes are reasonable under the circumstances and given the information available at this time. Refer to the notes to the unaudited pro forma combined financial statements included elsewhere in this prospectus for a discussion of adjustments reflected in the unaudited pro forma combined financial statements. Consequently, the financial information included here may not necessarily reflect our financial position, results of operations and cash flows in the future or what our financial position, results of operations and cash flows would have been had we been an independent, publicly traded company during the periods presented.

For a better understanding, this section should be read in conjunction with the discussion in "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the "Unaudited Pro Forma Combined Financial Statements" and corresponding notes and the audited combined financial statements and corresponding notes included elsewhere in this prospectus.

	Year Ended December 31,		
(in thousands)	2017	2018	Pro Forma 2018 (unaudited)
Statement of Operations:			
Cost and expenses			
Research and development	$ 78,803	$ 87,716	$ 87,716
General and administrative	15,119	27,536	35,769
Net loss	$ (93,922)	$ (115,252)	$ (123,485)

	As of December 31,		
(in thousands)	2017	2018	Pro Forma 2018 (unaudited)
Balance Sheet:			
Total assets	$ 5,470	$ 7,401	$ 167,882
Accrued research and development costs	4,905	5,261	5,261
Total current liabilities	$ 14,037	$ 17,846	$ 16,365

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RISK FACTORS

You should consider carefully the following risks and uncertainties, together with all the other information in this prospectus, including our financial statements and notes thereto, when evaluating our common stock. The impact from these risks and uncertainties may be materially adverse to our business, prospects, financial condition and results of operations. The risks described below are not the only risks we face. Additional risks and uncertainties not currently known to us or those we currently view to be immaterial also may materially harm our business, prospects, financial condition and results of operations. As a result, the trading price of our common stock could decline, which could decrease the value of the shares you hold.

Risks Related to Our Financial Position and Capital Needs

Because we are a clinical-stage biopharmaceutical company with a limited operating history and no products approved for commercial sale, valuing our business and predicting our prospects is challenging.

We are a clinical-stage biopharmaceutical company that was incorporated in 2018. Our business was conducted within Ironwood prior to that time, and we have no history as an independent company prior to the completion of the separation. We are developing a pipeline of sGC stimulators, but we have no products approved for commercial sale, and we have never generated revenue from product sales. Our operating activities to date have been limited primarily to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates and conducting early stage clinical trials for our most advanced product candidates, praliciguat, olinciguat and IW-6463.

To date, we have not obtained marketing approval for any of our product candidates, engaged, on our own or through a third party, in commercial scale manufacturing, or conducted significant sales and marketing activities necessary for the commercialization of our product candidates. Our short operating history offers limited insight into our prospects for success or even viability and we expect our operating results to be subject to frequent fluctuations. We will encounter challenges frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully navigate such challenges. If we do not successfully address the challenges we face, our business, prospects, financial condition and results of operations will be materially harmed.

Our business has incurred significant losses and we anticipate that we will continue to incur significant losses for the foreseeable future. We have never generated revenue from product sales and may never be profitable.

Our business has incurred operating losses due to costs incurred in connection with our research and development activities and general and administrative expenses associated with our operations. Our net losses for the years ended December 31, 2017 and 2018 were $93.9 million and $115.3 million, respectively. As of December 31, 2018, we had a net parent investment of $(10.4) million. We expect to incur significant losses for several years, as we continue our research activities and conduct development of, and seek regulatory approvals for, our product candidates.

Our ability to generate revenue from our product candidates and achieve profitability depends on our ability, alone or with strategic partners, to complete the development of, and obtain the necessary regulatory and essential pricing and reimbursement approvals to commercialize, our product candidates. We do not know when we will generate revenues from sales of our products, if ever.

We expect to continue to incur significant losses for the foreseeable future. Our expenses could increase beyond expectations if we are required by the FDA, the European Medicines Agency, or the EMA, or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Even if one or more of the product candidates that we

develop is approved for commercial sale, we may never generate revenue in amounts sufficient to achieve and maintain profitability.

We will need to raise additional funding to advance our product candidates, which may not be available on acceptable terms, or at all. Failure to obtain capital when needed may force us to delay, limit or terminate our product development efforts or other operations. Raising additional capital may dilute our existing shareholders, restrict our operations or cause us to relinquish valuable rights.

Following the completion of the separation and the closing of the private placement, our cash and cash equivalents are approximately $165.0 million, after the payment of certain separation-related expenses. Our management believes that such cash and cash equivalents will be sufficient to fund our operating expenses and capital expenditure requirements through the first quarter of 2021. However, we will require significant additional funding to advance our product candidates, alone or with strategic partners, through clinical studies and to seek marketing approval, as well as to continue advancing our research and development efforts with our other product candidates. We may also need to raise additional funds sooner than currently anticipated if we choose to pursue additional indications or geographies for our product candidates, identify additional product candidates to advance through clinical development or otherwise expand more rapidly than we presently anticipate. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution.

We may seek to raise such capital through public or private equity or debt financings. Raising funds in the current economic environment may present substantial challenges, and future financing may not be available in sufficient amounts or on acceptable terms, if at all. The terms of any financing may harm existing shareholders, and the issuance of additional securities, whether equity or debt, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities may dilute the ownership of existing shareholders. The incurrence of indebtedness would result in increased fixed payment obligations, and we may agree to restrictive covenants, such as limitations on our ability to incur additional debt or limitations on our ability to acquire, sell or license intellectual property rights that could impede our ability to conduct our business. Regardless of the terms of our debt or equity financing, our agreements and obligations under the tax matters agreement with Ironwood limits our ability to issue stock. See "—Risks Related to the Separation and the Private Placement."

We may also seek funds through collaborations, strategic alliances, or licensing arrangements with third parties, and such agreements may involve relinquishing rights to our product candidates or technologies, future revenue streams, research programs or products candidates or to grant licenses on terms that may not be favorable to us. Such arrangements will limit our participation in the success of any of our product candidates that receive regulatory approval.

If we are unable to raise capital when needed or on reasonable terms, we may curtail, delay or discontinue our research or development programs, scale back or cease any commercialization efforts or wind down our business. In addition, such additional fundraising efforts may divert our management from their day-to-day activities, which may impede our ability to develop and commercialize our product candidates.

Risks Related to the Discovery, Product Development and Regulatory Approval of Our Product Candidates

The "target-to-disease" approach we are taking to discover and develop product candidates targeting cGMP, may never lead to marketable products.

We have concentrated our product research and development efforts to date on a "target-to-disease" approach to the treatment of diseases involving the cGMP pathway and/or sGC

signaling, so our future success depends on the successful development of our pipeline of sGC stimulators. The scientific evidence to support the feasibility of developing our product candidates is both preliminary and limited. If we do not successfully develop and commercialize product candidates based upon our "target-to-disease" approach, we will not become profitable and the value of our common stock may decline.

Further, our focus solely on developing a pipeline of sGC stimulators, instead of multiple, more proven technologies, increases the risks associated with the ownership of our common stock. If we are not successful in developing any product candidates using our sGC platform, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and implement successfully an alternative product development strategy, which would materially harm our business, prospects, financial condition and results of operations.

Research and development of biopharmaceutical products is inherently risky. We may encounter substantial delays in our clinical studies, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Our current product candidates are at an early stage of development. Our business depends heavily on successful preclinical development, clinical testing, regulatory approvals and commercialization of our lead product candidates, olinciguat, praliciguat and IW-6463. These and our other product candidates, as well as any we may discover in the future, will require substantial additional development and testing, as well as regulatory approvals, prior to commercialization.

Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical and clinical studies that our product candidates are both safe and effective for use in each target indication. Each product candidate must demonstrate an adequate benefit-risk profile for its intended use in its intended patient population. In some instances, significant variability in safety or efficacy appear in different clinical studies of the same product candidate due to numerous factors, including changes in study protocols, differences in the number and characteristics of the enrolled subjects, variations in the dosing regimen and other clinical study parameters or the dropout rate among study participants. Product candidates in later stages of clinical studies often fail to demonstrate adequate safety and efficacy despite promising preclinical testing and earlier clinical studies. A number of companies in the biopharmaceutical industry have suffered significant setbacks in later-stage clinical studies. Most product candidates that begin clinical studies are never approved for commercialization by regulatory authorities.

If we encounter difficulties in enrolling subjects in our clinical studies, we could be delayed or prevented from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical studies of our product candidates is critical to our success. The timing of our clinical studies depends in part on the speed at which we can recruit patients to participate in testing our product candidates. The estimated incidence of our target indications, including SCD, DN and HFpEF, the initial target indications for our lead product candidates, varies considerably. Determining the incidence of these conditions, including in specific geographies or demographic groups, is challenging. The lower the actual incidence of these conditions, the more challenges we will encounter enrolling subjects in our clinical studies, which could delay development of our product candidates. Clinical trial enrollment may also encounter difficulties for a variety of other reasons. The number of patients eligible for a clinical trial may be substantially limited by stringent eligibility criteria in a study protocol, such as the inclusion of biomarker-driven identification or other highly specific criteria related to stage of disease progression or to specific patient reported outcome measures. The number of patients required to power the statistical analysis of the study's endpoints may be very large leading to an extended enrollment period. Issues such as the proximity of subjects to a study site, the complexity of the study design, our ability to recruit

investigators with appropriate skill and experience, competing clinical studies for similar therapies or targeting similar subjects, perceptions of the benefit-risk profile of the product candidate relative to other available therapies or product candidates, and ability to obtain and maintain institutional review board, or IRB, or ethics committee, or EC, approvals and patient consents all could have a substantial impact on the timing of clinical trial enrollment. If we are unable to enroll sufficient subjects in clinical studies in a timely way, obtaining study results will be delayed, which may harm our business, prospects, financial condition and results of operations.

The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates, we will be unable to generate product revenue and our business will be substantially harmed.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable, typically takes many years following the commencement of clinical studies and depends upon numerous factors, including the type and complexity of the product candidates involved. Regulatory authorities have substantial discretion in the approval process and may refuse to accept an application for review, or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. We have not requested or obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval. Furthermore, although we have received fast track designation for our product candidate praliciguat for the treatment of patients with HFpEF, this designation, or any other expedited approval designation that we may receive, does not change the standards for approval and may not ultimately expedite the development or approval process.

Our ongoing clinical studies may not be completed on schedule, and our planned clinical studies may not begin on schedule, if at all. The completion or commencement of clinical studies can be delayed or prevented for a number of reasons, including, among others:

- the FDA or other regulatory bodies may not authorize us or our investigators to commence planned clinical studies, or require that we suspend ongoing clinical studies through imposition of clinical holds;
- negative results from our ongoing studies or other industry studies involving product candidates modulating the same or similar mechanism of action;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical study sites, the terms of which can be subject to considerable negotiation and may vary significantly among different CROs and study sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical studies, for example delays in the manufacturing of sufficient supply of finished drug product;
- difficulties obtaining EC or IRB approval to conduct a clinical study at a prospective site or sites;
- challenges in recruiting and enrolling subjects to participate in clinical studies, the proximity of subjects to study sites, eligibility criteria for the clinical study, the nature of the clinical study protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical study programs for similar indications;
- severe or unexpected drug-related side effects experienced by subjects in a clinical study;

- the presence of unanticipated metabolites in subjects in a clinical study may require considerable preclinical and clinical assessment;
- we may decide, or regulatory authorities may require us, to conduct additional clinical studies or abandon product development programs;
- delays in validating, or inability to validate, any endpoints utilized in a clinical study;
- the FDA may disagree with our clinical study design and our interpretation of data from clinical studies, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical studies;
- reports from preclinical or clinical testing of other competing candidates that raise safety or efficacy concerns; and
- difficulties retaining subjects who have enrolled in a clinical study but may be prone to withdraw due to rigors of the clinical studies, lack of efficacy, side effects, personal issues, or loss of interest.

Clinical studies may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical study may be suspended or terminated by us, the FDA or other comparable authorities, the IRBs or ECs at the sites where the IRBs or ECs are overseeing a clinical study, a data and safety monitoring board overseeing the clinical study at issue or other regulatory authorities due to a number of factors, including, among others:

- failure to conduct the clinical study in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical study operations or study sites by the FDA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including in response to the imposition of a clinical hold;
- unforeseen safety issues, including any that could be identified in our ongoing studies, adverse side effects or lack of effectiveness;
- changes in government regulations or administrative actions;
- problems with clinical supply materials; and
- lack of adequate funding to continue clinical studies.

In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our treatment candidates. Even if regulatory approval is secured for any of our product candidates, the terms of such approval may limit the use of any approved product, which will limit its prospects for commercialization, which could have a material and adverse effect on our business, prospects, financial condition and results of operations.

Our product candidates may cause undesirable side effects that delay or prevent their regulatory approval, result in label restrictions or result in harmful consequences.

The most commonly reported adverse events in the clinical studies for olinciguat were headaches, tachycardia, dizziness, nausea, vomiting and hypotension. The most commonly reported adverse events in the clinical studies for praliciguat were headaches, tachycardia, dizziness, nausea, vomiting and hypoglycemia. A single serious adverse event of upper gastrointestinal hemorrhage occurred in a patient receiving praliciguat in a Phase 2a study and was determined to be study drug related. In addition, the pharmacology of sGC stimulation is known to cause certain side effects. For example, the label for ADEMPAS® (riociguat), the only FDA-approved sGC stimulator to date, indicates that ADEMPAS® can cause, among other side effects, serious birth defects if taken while pregnant, reduced

blood pressure and increased risk of bleeding. These side effects and any other undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical studies and could result in restrictive label language or delay or denial of regulatory approval.

Clinical studies by their nature utilize a defined sample of the potential enrolled subjects. With a limited number and variety of patients and limited duration of exposure, rare and severe side effects of our product candidates may only be uncovered when a significantly larger number and variety of patients are exposed to the product following commercialization. If our product candidates receive marketing approval, and we or others identify undesirable side effects caused by such product candidates (or any other similar products) after such approval, a number of potentially harmful consequences could result, including:

- regulatory authorities may withdraw their approval of the product;
- regulatory authorities may require modification to the label, such as addition of a special warning, or boxed warning, about risks or use or addition of contraindications;
- we may be required to change the way the product is distributed or administered and conduct additional clinical studies;
- we may be required to adopt a potentially restrictive risk evaluation and mitigation strategy with elements to assure safe use, or a Risk Evaluation and Management plan, or REMS, with elements to assure safe use, or ETASU, in the United States and the likelihood that we may be required to adopt a REMS may be increased given ADEMPAS was required to adopt a REMS;
- we may be required to conduct additional post-marketing studies;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide or be forced to remove a product from the marketplace;
- we could be sued and held liable for injuries caused or purportedly caused by use or ingestion of a product;
- the commercialization potential may be harmed; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and could significantly harm our business, prospects, financial condition and results of operations.

Changes in regulatory requirements, FDA guidance or unanticipated events during our preclinical studies and clinical studies of our product candidates may occur, which may result in changes to preclinical or clinical study protocols or additional preclinical or clinical study requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance or unanticipated events during our preclinical studies and clinical studies may force us to amend preclinical studies and clinical study protocols or the FDA may impose additional preclinical studies and clinical study requirements. Amendments or changes to our clinical study protocols would require resubmission to the FDA and IRBs for review and approval, which may increase the cost or delay the timing or successful completion of clinical studies. Similarly, amendments to our preclinical studies may increase the cost or delay the timing or successful completion of those preclinical studies. If we experience delays completing, or if we terminate, any of our preclinical or clinical studies, or if we are required to conduct additional

preclinical or clinical studies, the commercial prospects for our product candidates may be harmed and our ability to generate product revenue will be delayed.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

In order to market any product outside of the United States, we must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of other countries. Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA or other comparable foreign regulatory authority grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical or clinical studies, as studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States, as well as other risks. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our product candidates is also subject to approval.

Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair our ability to market our product candidates in such countries. Any such impairment would reduce the size of our potential market, which could have a material adverse impact on our business, prospects, financial condition and results of operations.

Orphan drug status may not ensure that we have market exclusivity in a particular market, and we could lose orphan market exclusivity if another drug is approved first using the same method of action or demonstrates clinical superiority.

We may pursue orphan drug status for certain of our pipeline programs. In June 2018, olinciguat received orphan drug designation for the treatment of patients with SCD. In the United States, a product candidate with orphan drug status qualifies for market exclusivity for seven years after FDA approval, unless a chemically identical competing product for the same indication is proven to be "clinically superior," that is, safer, more effective or significantly more convenient. Thus, if olinciguat or our other product candidates is granted regulatory approval in the United States, the FDA may not approve a competing generic product during the market exclusivity period. In Europe, EMA regulations provide ten-year marketing exclusivity for orphan drugs, subject to certain exceptions, including the demonstration of "clinically relevant superiority" by a similar medicinal product. EMA orphan marketing exclusivity applies to drug products for the same indication that use the same method of action but can be chemically dissimilar. If olinciguat or our other product candidates were to fail to obtain orphan drug status, or lose such status after it is obtained, or the marketing exclusivity that such status provides, our business, prospects, financial condition and results of operations could be materially harmed.

Risks Related to Our Reliance on Third Parties

We rely, and expect that we will continue to rely, on third parties to conduct any preclinical or clinical studies for our product candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We do not have the ability to independently conduct clinical studies. We rely on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct clinical studies on our product candidates. We rely heavily on these parties for execution of clinical studies for our product candidates and can control only certain aspects of their activities. As a result, we have less direct control over the conduct, timing and completion of these clinical studies and the management of data developed through clinical studies than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may have staffing difficulties, fail to comply with contractual obligations, experience regulatory compliance issues, undergo changes in priorities, become financially distressed or form relationships with other entities, some of which may be our competitors.

These factors may materially impede the willingness or ability of third parties to conduct our clinical studies and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our clinical studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific requirements and standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with regulations and guidelines, including good clinical practices, or GCPs, for conducting, monitoring, recording and reporting the results of clinical studies to ensure that the data and results are scientifically credible and accurate, and that the study patients are adequately informed of the potential risks of participating in clinical studies. These regulations are enforced by the FDA and comparable foreign regulatory authorities for any products in clinical development. The FDA enforces GCP regulations through periodic inspections of clinical study sponsors, principal investigators and study sites. If we and our CROs or our investigators fail to comply with applicable GCPs, the clinical data generated in our clinical studies may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical studies before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical studies comply with GCPs. In addition, our clinical studies must be conducted with product candidates produced under current good manufacturing practice, or GMP, regulations and will require a large number of test patients. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical studies, which would delay the regulatory approval process and could also subject us to enforcement action up to and including civil and criminal penalties.

Although we design our product candidate clinical studies, CROs conduct all of the clinical studies. As a result, many important aspects of the execution of our drug development programs are outside of our direct control. In addition, the CROs may not perform all of their obligations under arrangements with us or in compliance with regulatory requirements, but we remain responsible and are subject to enforcement action that may include civil penalties and criminal prosecution for any violations of FDA laws and regulations during the conduct of our clinical studies. If the CROs do not perform clinical studies in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development and commercialization of our product candidates may be delayed or our development program materially and irreversibly harmed. We may fail to control the amount and timing of resources these CROs devote to our program or our clinical products. If we are unable to rely on clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of our clinical studies and this could significantly delay commercialization and require significantly greater expenditures.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any clinical studies such CROs are associated with may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, we believe that our financial results and the commercial prospects for our product candidates in the approved indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We rely completely on third-party suppliers to manufacture our non-clinical and clinical drug supplies for our product candidates, and we intend to rely on third parties to produce commercial supplies of any product candidates that are approved.

We do not currently have, nor do we plan to acquire, the infrastructure or capability to internally manufacture the clinical drug supply of our product candidates, or any future product candidates, for use in the conduct of our clinical studies, and we lack the internal resources and the capability to manufacture any product candidates on a clinical or commercial scale. We depend on third-party contract manufacturing organizations, or CMOs, for all of our requirements of raw materials, drug substance and drug product for our ongoing clinical trials of praliciguat, olinciguat and IW-6463. We do not have long-term supply agreements in place with our CMOs and each batch of our product candidates is individually contracted under a services agreement on a purchase order basis. We expect to continue to rely on CMOs for the supply of praliciguat, olinciguat and IW-6463 for later-stage development and commercialization, as well as for the supply of any other product candidates that we may identify, and we may not be able to enter into long-term supply agreements with such CMOs on favorable terms. As a result, we are subject to price fluctuations for our clinical drug supplies. If the prices charged by these CMOs increase, our business, prospects, financial condition and results of operations could be materially harmed.

In addition, the facilities used by our contract manufacturers to manufacture the active pharmaceutical ingredient and final drug product must complete a pre-approval inspection by the FDA and other comparable foreign regulatory agencies to assess compliance with applicable requirements, including current GMP, after we submit our new drug application, or NDA, or relevant foreign regulatory submission to the applicable regulatory agency. If the FDA or an applicable foreign regulatory agency determines now or in the future that these facilities are noncompliant, we may need to find alternative manufacturing facilities, which would impede our ability to develop, obtain regulatory approval for or market our product candidates.

Our reliance on third parties requires us to share our confidential information, including trade secrets and know-how, which increases the possibility that our confidential information will be misappropriated or disclosed.

Because we rely on third parties to manufacture our product candidates, and because we collaborate with various CROs to conduct our clinical trials, we must, at times, share our trade secrets or know-how with them. We seek to protect our confidential information, including know-how and trade secrets, in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors and consultants prior to beginning our collaborations or disclosing confidential information to such parties. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets and know-how. Despite these contractual provisions, the need to share our confidential information with third parties increases the risk that confidential information such as trade secrets and know-how becomes known by our

competitors, is inadvertently incorporated into the technology of others, or is disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our confidential information including know-how and trade secrets, a competitor's discovery of our confidential information or other unauthorized use or disclosure could impair our competitive position and may have a material adverse effect on our business, prospects, financial condition and results of operations.

Any collaboration or license arrangements that we may enter into in the future may not be successful, which could impede our ability to develop and commercialize our product candidates.

We may seek collaboration or license arrangements for the commercialization, or potentially for the development, of certain of our product candidates depending on the merits of retaining commercialization rights for ourselves as compared to entering into collaboration or license arrangements. We will face, to the extent that we decide to enter into such arrangements, significant competition in seeking appropriate partners. Moreover, collaboration and license arrangements are complex and time-consuming to negotiate, document, implement and maintain. We may not be successful in our efforts to establish and implement such arrangements should we so chose to enter into them. The terms of any collaborations, licenses or other arrangements that we may establish may not be favorable to us.

Any future collaboration or license arrangements that we enter into may not be successful. The success of such arrangements will depend heavily on the efforts and activities of our partners. Collaboration and license arrangements are subject to numerous risks, which may include risks that:

- partners have significant discretion in determining the efforts and resources that they will apply to collaborations;
- a partner with marketing, manufacturing and distribution rights to one or more products may not commit sufficient resources to or otherwise not perform satisfactorily in carrying out these activities;
- partners may not properly maintain or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liability;
- collaboration and license arrangements may be terminated, and, if terminated, this may result in a need for additional capital to pursue further development or commercialization of the applicable current or future product candidates;
- partners may own or co-own intellectual property covering products that results from our collaborating with them, and in such cases, we would not have the exclusive right to develop or commercialize such intellectual property;
- disputes may arise with respect to the ownership of any intellectual property developed pursuant to our collaboration or license arrangements; and
- a partner's sales and marketing activities or other operations may not be in compliance with applicable laws resulting in civil or criminal proceedings.

Risks Related to Our Intellectual Property Rights

If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents that are sufficient to protect our product candidates, others could compete against us more directly, which would have a material adverse impact on our business, prospects, financial condition and results of operations.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection in the United States and other countries for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, should they issue, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking patents intended to cover our products and compositions, their methods of use and any other inventions that are important to the development of our business.

As of April 2, 2019, we had 10 issued U.S. patents, 21 pending U.S. patent applications, eight pending Patent Cooperation Treaty, or PCT, applications, and numerous foreign patents and pending patent applications. Our issued U.S. and foreign patents covering olinciguat expire between 2031 and 2034 and our issued U.S. and foreign patents covering praliciguat also expire between 2031 and 2034, in each case subject to patent term extensions. We have no issued patents covering IW-6463, and our pending patent applications relating to IW-6463, if issued, will expire in 2037 or later. See "Business—Intellectual Property." We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

The patent positions of biotechnology and pharmaceutical companies, including ours, involve complex legal and factual questions, which in recent years have been the subject of much litigation, and, therefore, the issuance, scope, validity, enforceability and commercial value of any patent claims that we may obtain cannot be predicted with certainty. Our pending patent applications may not be granted as issued patents in any particular jurisdiction and, even if they do, these patents may not include claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage.

Even if our patent applications are issued, competitors and other third parties may infringe, misappropriate or otherwise violate our patents and other intellectual property rights. We may not be able to prevent infringement, misappropriation or other violations of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the attention of our management and key personnel from our business operations

Moreover, our patents, if issued, may be challenged, deemed unenforceable, invalidated or circumvented in the United States and abroad. U.S. patents and patent applications may also be subject to interference, derivation, *ex parte* reexamination, post-grant review, or *inter partes* review proceedings, supplemental examination and challenges in district court. Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our involvement in litigation or interference proceedings may fail and, even if successful, may result in substantial costs, and distract our management and other employees. Furthermore, an adverse decision in an interference or derivation proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize our product candidates.

Patents may also be subjected to opposition, post-grant review or comparable proceedings lodged in various foreign, both national and regional, patent offices or courts. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover our product candidates or competitive products. In addition, such proceedings may be costly. Thus, any patents, should they issue, that we may own or exclusively license may not provide any protection against competitors.

Furthermore, though a patent, if it were to issue, is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate protection to exclude competitors from making similar products. Even if a patent issues and is held to be valid and enforceable, competitors may be able to design around or circumvent our patents, such as by using pre-existing or newly developed technology or products in a non-infringing manner. If these developments were to occur, they could have a material adverse effect on our business, prospects, financial condition and results of operations.

Any litigation to enforce or defend our patent rights, even if we were to prevail, would be costly and time-consuming and would divert the attention of our management and key personnel from our business operations. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

In addition, proceedings to enforce or defend our patents, if and when issued, puts our patents at risk of being invalidated, held unenforceable or not infringed, or interpreted narrowly. Such proceedings could also provoke third parties to assert counterclaims against us, including that some or all of the claims in one or more of our patents are invalid, not infringed or unenforceable. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions of a patent include allegations that someone connected with prosecution of the patent application that matured into the patent withheld relevant information from the U.S. Patent and Trademark Office, or the USPTO, or made a misleading statement, during prosecution of the patent application. In an infringement proceeding, a court may disagree with our allegations and refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question, or may decide that a patent of ours is invalid or unenforceable. An adverse result in any litigation, defense or post-grant proceedings could result in one or more of our patents being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it would have a material adverse effect on the price of our common stock.

The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates.

If any of our patents, if and when issued, covering our product candidates are invalidated or found not infringed or unenforceable, our business, prospects, financial condition and results of operations could be materially harmed.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing our product candidates, if approved.

Our success will depend in part on our ability to operate without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. Other parties may allege that our product candidates or the use of our technologies infringes or otherwise violates patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to compositions, materials, formulations, methods of manufacture or methods for treatment related to our product candidates. Because patent applications can take many years to issue, third parties may have currently pending patent applications which may later result in issued patents that our product candidates may infringe, or which such third parties claim are infringed by our technologies.

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain and cannot be adequately quantified in advance. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either does not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our products. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing our product candidates. Any claim relating to intellectual property infringement that is successfully asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license.

Any of these risks coming to fruition could have a material adverse effect on our business, prospects, financial condition and results of operations.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

Our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors enter into confidentiality and intellectual property assignment agreements with us or have entered into confidentiality and intellectual property assignment agreements with Ironwood. We seek to have inventions assigned to us by the person rendering services. However, we may not be able to enter into these agreements with all parties or these agreements may not be honored and may not effectively assign intellectual property rights to us.

Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we

are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions over the lifetime of our owned patents and applications. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors or other third parties might be able to enter the market earlier than would otherwise have been the case and this circumstance could have a material adverse effect on our business, prospects, financial condition and results of operations.

We may not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

The statutory deadlines for pursuing patent protection in individual foreign jurisdictions are based on the priority date of each of our patent applications and we may not timely file foreign patent applications. Thus, for each of the patent families that we believe provide coverage for our product candidates, we will need to decide whether and where to pursue protection outside the United States. Filing and prosecuting patent applications, and defending patents on product candidates in all countries and jurisdictions throughout the world would be prohibitively expensive, and so we are unlikely to pursue and maintain patents in all countries worldwide. As such, competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products.

The laws of some foreign countries may not protect intellectual property rights to the same extent as the laws of the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States even if we have a patent in that jurisdiction. Further, a competitor may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology or pharmaceuticals. This could make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of or marketing of competing products in violation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

If we do not obtain additional protection under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, and similar foreign legislation by extending the patent terms and obtaining data exclusivity for our product candidates, our business, prospects, financial condition and results of operations may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, one or more of the U.S. patents we own may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent term extension as compensation for patent term lost during the FDA regulatory review process. A maximum of five years can be restored to the eligible patent. In all cases, the total patent life for the product with the patent extension cannot exceed 14 years from the product's approval date, or in other words, 14 years of potential marketing time. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain a patent term extension or the term of any such extension is less than we request, the duration of patent protection we obtain for our product candidates may not provide us with any meaningful commercial or competitive advantage, our competitors may obtain approval of competing products earlier than they would otherwise be able to do so, and our ability to generate revenues could be harmed.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation: the Leahy-Smith America Invents Act, or the America Invents Act. The America Invents Act includes a number of significant changes to U.S. patent law. These provisions affect the way patent applications will be prosecuted and may also affect patent litigation. It is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any patents that may issue from our patent applications, all of which could have a material adverse effect on our business, prospects, financial condition and results of operations.

In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on these and other decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce any patents that may issue in the future.

We may be subject to damages resulting from claims that we or our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers.

Our employees may have been previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We also engage advisors and consultants who are concurrently employed at universities or who perform services for other entities.

We may be subject to claims that we or our employees, advisors or consultants have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third party. We may be subject to claims that an employee, advisor or consultant performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying money claims, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our product candidates, which would materially harm our commercial development efforts.

Risks Related to the Future Commercialization of Our Product Candidates

The incidence and prevalence for target patient populations of our product candidates have not been established with precision. If the market opportunities for our product candidates are smaller than we estimate, or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability may be harmed.

The incidence and prevalence for all the conditions we aim to address with our programs are unknown. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations or market research, and may prove to be incorrect. Further, new trials may change the estimated incidence or prevalence of these diseases. The total addressable market across all of our product candidates will ultimately depend upon, among other things, the diagnosis criteria included in the final label for each of our product candidates, if approved for sale for these indications, acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients in the United States and other major markets and elsewhere may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our products or new patients may become increasingly difficult to identify or gain access to, all of which would harm our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market any product candidates, if approved, we may not be successful in commercializing those product candidates if and when they are approved.

We do not currently have an infrastructure for the sale, marketing, market access, patient service and distribution of pharmaceutical products. In order to market our product candidates, if approved by the FDA or any other regulatory authority outside the United States, we must build our sales, marketing, managerial and other non-technical capabilities, or arrange with third parties to perform these services. There are risks involved with both establishing our own commercial capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force or reimbursement specialists is expensive and time-consuming and could delay any

product candidate launch. If commercialization is delayed or does not occur, we would have prematurely or unnecessarily incurred such expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our commercialization personnel.

If we enter into arrangements with third parties to perform sales, marketing, commercial support and distribution services, our product revenue or the profitability of product revenue may be lower than if we were to market and sell any products we may develop ourselves. In addition, we may fail to enter into arrangements with third parties to commercialize our product candidates or may be unable to do so on terms that are favorable to us. We may have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish commercialization capabilities successfully, either on our own or in collaboration with third parties, or if we are unable to do so on commercially reasonable terms, we will not be successful in commercializing our product candidates if approved and our business, prospects, financial condition and results of operations will be materially harmed.

Even if we obtain regulatory approval for our product candidates, our product candidates may not achieve broad market acceptance by patients, physicians, healthcare payors or others in the medical community, which would limit the revenue that we generate from their sales.

The future commercial success of our product candidates, if approved by the FDA or other applicable regulatory authorities outside the United States, will depend upon the awareness and acceptance of our product candidates among the medical community, including patients, physicians and healthcare payors. If any of our product candidates are approved but do not achieve an adequate level of acceptance by patients, physicians, healthcare payors and others in the medical community, we may not generate sufficient revenue to become, or remain, profitable. Market acceptance of our product candidates, if approved, will depend on a number of factors, including, among others:

- the efficacy and safety of our approved product candidates as demonstrated in clinical trials;
- the clinical indications for which our product candidates are approved;
- limitations or warnings contained in the labeling approved for our product candidates by the FDA or other applicable regulatory authorities;
- any restrictions on the use of our products together with other medications or restrictions on the use of our products in certain types of patients;
- the prevalence and severity of any adverse effects associated with our product candidates;
- the size of the target patient population, and the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the safety, efficacy, cost and other potential advantages of our approved product candidates compared to other available therapies;
- our ability to generate cost effectiveness data that supports a profitable price;
- our ability to obtain sufficient reimbursement and pricing by third-party payors and government authorities;
- the willingness of patients to pay out-of-pocket in the absence of sufficient payor coverage.
- the effectiveness of our sales and marketing strategies; or
- publicity concerning our products or competing products and treatments.

If our product candidates are approved but do not achieve an adequate level of acceptance by patients, physicians and payors, we may not generate sufficient revenue from our product candidates to

become or remain profitable. Before granting reimbursement approval, healthcare payors may require us to demonstrate that our product candidates, in addition to treating these target indications, also provide incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of our product candidates may require significant resources and may never be successful.

Reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our products profitably. Price controls may be imposed in foreign markets, which may harm our future profitability.

Market acceptance and sales of any approved product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors and government authorities and may be affected by existing and future health care reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. Reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is: a covered benefit under its health plan; safe, effective and medically necessary; appropriate for the specific patient; cost-effective; and neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor. We or our partners may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available for any of our product candidates. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products. In addition, in the United States, third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse patients for their use of newly approved drugs, which in turn will put pressure on the pricing of drugs.

In some countries, particularly member states of the European Union, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our partners may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed.

If we fail to comply with healthcare and other regulations, we could face substantial penalties and our business, prospects, financial condition and results of operations could be harmed.

The product candidates that we are evaluating in clinical studies are subject to certain federal and state healthcare laws and regulations that may affect our business. These laws and regulations include:

- federal healthcare program anti-kickback laws, which prohibit, among other things, persons from offering, soliciting, receiving or providing remuneration, directly or indirectly, as an inducement or reward for their past, current or potential future prescribing, purchase, use, recommending for use, referral, formulary placement, or dispensing of our products;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters and which also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;

- the Federal Food, Drug, and Cosmetic Act, which among other things, strictly regulates drug product and medical device research, development, and marketing, prohibits manufacturers from marketing or promoting such products prior to approval; and

- state law equivalents of the above federal laws, such as anti-kickback laws, state transparency laws, state laws limiting interactions between pharmaceutical manufacturers and members of the healthcare industry and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts.

In addition, we may be subject to privacy and security laws in the various jurisdictions in which we operate, obtain or store personally identifiable information. For example, if we conduct clinical studies in any of the member states of the European Union, the processing of personal data in the European Economic Area, or the EEA, is subject to the 1995 Data Protection Directive, imposing strict obligations and restrictions on the ability to collect, analyze and transfer personal data. In May 2018, the General Data Protection Regulation, or the GDPR, took effect, increasing our obligations with respect to clinical studies conducted in the EEA and increasing the scrutiny applied by clinical study sites located in the EEA to transfers of personal data from such sites to countries that are considered by the European Commission to lack an adequate level of data protection, such as the United States. The compliance obligations imposed by the GDPR may increase our cost of doing business. In addition, the GDPR imposes substantial fines for breaches of data protection requirements, and it confers a private right of action on data subjects for breaches of data protection requirements.

If our operations are found to be in violation of any of the laws described above or any other laws, rules or regulations that apply to us, we will be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could impede our ability to operate our business and our financial results. We cannot be certain that compliance programs will address all areas of potential exposure and the risks in this area cannot be entirely eliminated, particularly because the requirements and government interpretations of the requirements in this space are constantly evolving. Any action against us for violation of these laws, rules or regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business, as well as damage our business or reputation. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, fraud and reporting laws may prove costly.

We face significant competition in an environment of rapid technological and scientific change, and our competitors may achieve regulatory approval before us or develop therapies that are safer, more advanced or more effective than ours, which may harm our ability to successfully market or commercialize any product candidates we may develop and ultimately harm our financial condition.

Our future success depends on our ability to demonstrate and maintain a competitive advantage with respect to the design, development and commercialization of our product candidates. Our objective is to design, develop and commercialize new products with superior efficacy, safety, tolerability and convenience. In many cases, our product candidates that we commercialize will compete with existing, market-leading products. The development and commercialization of new drug products is highly competitive. We may face competition with respect to any product candidates that we seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Bayer AG and Merck & Co., Inc., or Bayer/Merck, have an active collaboration on sGC and may be targeting some of the same indications through a similar mechanism of action with one sGC stimulator, ADEMPAS® (riociguat), which has been approved for the treatment of Pulmonary Arterial Hypertension, or PAH, and Chronic Thromboembolic Pulmonary Hypertension, or CTEPH. Bayer/Merck are also evaluating sGC product candidates in a number of indications, including vericiguat for the treatment of heart failure. Such sGC products may compete directly with our own product candidates in our target indications. Because Bayer/Merck already have experience conducting successful clinical trials and obtaining regulatory approvals for an sGC product, they may be able to conduct clinical trials and obtain regulatory approvals for additional product candidates and target indications more quickly or efficiently than we can.

Furthermore, we are aware of a number of other approved products and late-stage product candidates for the treatment of our target indications. Two products have been approved to reduce the acute complications of SCD, such as painful crises, hydroxyurea (marketed as DROXIA® or SIKLOS®, as well as other generic forms) and ENDARI®, and Novartis AG, or Novartis, Global Blood Therapeutics, Inc., Imara, Inc., Pfizer Inc., AstraZeneca plc, Micelle BioPharma, Inc., CRISPR Therapeutics AG / Vertex Pharmaceuticals, Inc., bluebird bio, Inc., Bioverativ/Sangamo, Modus Therapeutics AB, and Prolong Pharmaceuticals, LLC each have product candidates in various stages of clinical development for the treatment of SCD, any of which may compete with olinciguat, if approved. Similarly, three products have been approved for the treatment of DN, including AVAPRO®, CAPOTEN® and COZAAR®, and we are aware of late-stage clinical trials being conducted by Eli Lilly and Company / Boehringer Ingelheim GmbH, or Eli Lilly/Boehringer, AstraZeneca plc, and Bayer for the treatment of DN that might compete with praliciguat, if approved. Additionally, Janssen Pharmaceuticals conducted a late stage clinical-trial for INVOKANA for the treatment of kidney disease in patients with type 2 diabetes that was stopped early because of positive efficacy findings and has recently submitted an sNDA for chronic kidney disease in patients with type 2 diabetes. If approved, such product candidate may compete with praliciguat. Similarly, Novartis, Bayer/Merck, AstraZeneca plc, and Eli Lilly/Boehringer each have product candidates in late-stage clinical trials for the treatment HFpEF, any of which may also compete with praliciguat, if approved. If our product candidates do not obtain regulatory approvals in our target indications prior to these or any other competing product candidates, or if our product candidates do not demonstrate superior efficacy, safety or tolerability compared to these and any other approved therapeutics for our target indications, we may not be able to compete effectively.

Many of our current or potential competitors, either alone or with their strategic partners, have significantly greater financial resources and expertise in research and development, manufacturing,

preclinical testing, conducting clinical studies, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours and may obtain orphan product exclusivity from the FDA for indications our product candidates are targeting, which could result in our competitors establishing a strong market position before we are able to enter the market.

In addition, we could face litigation or other proceedings with respect to the scope, ownership, validity and/or enforceability of our patents relating to our competitors' products and our competitors may allege that our products infringe, misappropriate or otherwise violate their intellectual property. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. See "—Risks Related to Our Intellectual Property Rights."

The impact of healthcare reform and other governmental and private payor initiatives may harm our business.

Our revenue prospects could be affected by changes in healthcare spending and policy in the United States and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to health care availability, the method of delivery or payment for health care products and services could harm our business, operations and financial condition. There is significant interest in promoting health care reform, as evidenced by the enactment in the United States of the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act in 2010. It is likely that federal and state legislatures within the United States and foreign governments will continue to consider changes to existing health care legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect: the demand for any drug products for which we may obtain regulatory approval; our ability to set a price that we believe is fair for our products; our ability to obtain coverage and reimbursement approval for a product; our ability to generate revenues and achieve or maintain profitability; and the level of taxes that we are required to pay.

Our future growth may depend, in part, on our ability to commercialize our product candidates outside the United States, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability may depend, in part, on our ability to commercialize our product candidates outside the United States for which we may rely on partnerships with third parties. If we commercialize our product candidates outside the United States, we would be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for our product candidates outside the United States;
- our ability to gain reimbursement in foreign markets at a price that is profitable;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;

- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- the existence of additional potentially relevant third-party intellectual property rights;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of our product candidates could also be harmed by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

In light of the large population of patients with SCD who reside in foreign countries, our ability to generate meaningful revenues in those jurisdictions may be limited due to the strict price controls and reimbursement limitations imposed by governments outside of the United States.

In some countries, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies, or to meet other criteria for pricing approval. Given the significant portion of the population of patients with SCD who reside outside of the United States, if reimbursement of olinciguat, if approved, is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, prospects, financial condition and results of operations could be harmed.

If any of our product candidates obtain regulatory approval, additional competitors could enter the market with generic versions of such drugs, which may result in a material decline in sales of affected products.

Under the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or an ANDA, seeking approval of a generic copy of an approved, small-molecule innovator product. Under the Hatch-Waxman Act, a manufacturer may also submit an NDA that references the FDA's prior approval of the small-molecule innovator product. The Hatch-Waxman Act also provides for certain periods of regulatory exclusivity. These include, subject to certain exceptions, the period during which an FDA-approved drug is subject to orphan drug exclusivity. In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the "Orange Book." If there are patents listed in the Orange Book, a generic or NDA applicant that seeks to market its product before expiration of the patents must include in the ANDA a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents.

Accordingly, if any of our product candidates are approved, competitors could file ANDAs for generic versions of our small-molecule drug products or NDAs that reference our small-molecule drug products, respectively. If there are patents listed for our small-molecule drug products in the Orange Book, those ANDAs and NDAs would be required to include a certification as to each listed patent

indicating whether the ANDA applicant does or does not intend to challenge the patent. We cannot predict which, if any, patents in our current portfolio or patents we may obtain in the future will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any of our patents that are listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could immediately face generic competition and its sales would likely decline rapidly and materially.

Risks Related to Our Business Operations

Our prospects for success depend on our ability to retain our management team and to attract, retain and motivate qualified personnel.

We are highly dependent on our management, scientific and medical personnel, including our Chief Executive Officer, Peter M. Hecht, Ph.D., our President, Mark Currie, Ph. D, our Chief Financial Officer, William Huyett and our Head of Global Development, Christopher Wright, M.D., Ph.D. Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us on short notice. The loss of the services of any of our executive officers, other key employees and other scientific and medical advisors and an inability to find suitable replacements could result in delays in product development and harm our business. Pursuant to their employment arrangements, each of our executive officers, and other employees may voluntarily terminate their employment at any time, with or without notice. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior managers as well as junior, mid-level and senior scientific and medical personnel.

We may not be able to attract or retain qualified management and scientific personnel in the future due to the intense competition for a limited number of qualified personnel among biopharmaceutical, biotechnology, pharmaceutical and other businesses. Many of the other pharmaceutical companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than what we may be able to offer. We also experience competition for the hiring of scientific personnel from universities and research institutions. The failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. In addition, in order to induce employees to continue their employment with us, we have provided equity awards that vest over time and the value to our employees of such equity awards may be significantly affected by movements in our stock price that are beyond our control and may be at any time insufficient to counteract more lucrative offers from other companies. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize product candidates will be limited.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

As of April 1, 2019, we had 143 full-time employees. As we mature, we expect to expand our full-time employee base and to hire more consultants and contractors. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may

divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We face potential product liability exposure, and, if claims are brought against us, we may incur substantial liability.

The use of our product candidates in clinical studies and the sale of our products, if approved, exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others selling or otherwise coming into contact with our product candidates. For example, we may be sued if any product candidate we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things: withdrawal of subjects from our clinical studies; substantial monetary awards to patients or other claimants; decreased demand for our product candidates or any future product candidates following marketing approval, if obtained; damage to our reputation and exposure to adverse publicity; increased FDA warnings on product labels; litigation costs; distraction of management's attention from our primary business; loss of potential revenue; and the inability to successfully commercialize our product candidates or any future product candidates, if approved.

We maintain product liability insurance coverage for our clinical studies through both domestic and international insurance policies, subject to an annual coverage limit. Nevertheless, our insurance coverage may be insufficient to reimburse us for any expenses or losses we may suffer if a judgment or settlement exceeds available insurance proceeds. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may not be able to obtain this product liability insurance on commercially reasonable terms. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our stock price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our business, prospects, financial condition and results of operations could be materially harmed.

During the course of treatment, patients may suffer adverse events, including death, for reasons that may or may not be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our product candidates, if approved, or require us to suspend or abandon our commercialization efforts of any approved product candidates. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, prospects, financial condition and results of operations.

We will incur increased costs as a result of operating as a public company. If we fail to maintain proper and effective internal controls, our ability to produce accurate and timely financial statements could be impaired, which could result in sanctions or other penalties that would harm our business.

We are now subject to the reporting requirements of the Securities Exchange Act of 1934, or the Exchange Act, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and the rules and regulations of The Nasdaq Global Select Market, or Nasdaq. Our financial results historically were included within the consolidated results of Ironwood, and until the distribution, we had not been directly subject to reporting and other requirements of the Exchange Act and Section 404 of the Sarbanes-Oxley Act. We are an "emerging growth company" and a "smaller reporting company." For so long as we remain an emerging growth company, we will be exempt from Section 404(b) of the Sarbanes-Oxley Act, which requires auditor attestation to the effectiveness of internal control over financial reporting. We will cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total gross annual revenues of $1.07 billion or more; (ii) December 31, 2024, the last day of our fiscal year following the fifth anniversary of the date of the distribution; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including exemption from compliance with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on the exemptions available to us as an emerging growth company and/or smaller reporting company. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

We are, however, subject to Section 404(a) of the Sarbanes-Oxley Act. Beginning with our Annual Report on Form 10-K for the fiscal year 2020, we must include a management assessment of the effectiveness of our internal control over financial reporting. As of the expiration of our emerging growth company status and smaller reporting company status, we will be broadly subject to enhanced reporting and other requirements under the Exchange Act and Sarbanes-Oxley Act. This will require, among other things, annual management assessments of the effectiveness of our internal control over financial reporting and a report by our independent registered public accounting firm addressing these assessments. These and other obligations will place significant demands on our management, administrative and operational resources, including accounting and information technology resources. To comply with these requirements, we anticipate that we will need to further upgrade our systems, including duplicating computer hardware infrastructure, implement additional financial and management controls, reporting systems and procedures and hire additional accounting, finance and information technology staff. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costlier. If we are unable to do this in a timely and effective fashion, our ability to comply with our financial reporting requirements and other rules that apply to reporting companies could be impaired and our business, prospects, financial condition and results of operations could be harmed.

We may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no

evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls over financial reporting, we may not be able to produce timely and accurate financial statements. If that were to happen, our investors could lose confidence in our reported financial information, the market price of our stock could decline, and we could be subject to sanctions or investigations by the SEC or other regulatory authorities.

Unfavorable global economic conditions could harm our business, prospects, financial condition and results of operations.

Our results of operations could be harmed by general conditions in the global economy and in the global financial markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including, weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption. Any of the foregoing could harm our business, prospects, financial condition and results of operations.

Our internal computer systems, or those of our third-party CROs, CMOs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product candidates' development programs.

Despite the implementation of security measures, our internal computer systems and those of our third-party CROs, CMOs, business development partners and other contractors and consultants may be vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical study data for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. Insurance, may not be adequate to fully cover costs to restore data and resume normal working operations, which could harm our business, prospects, financial condition and results of operation.

Our employees may engage in misconduct or other improper activities, including violating applicable regulatory standards and requirements or engaging in insider trading, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and applicable foreign regulators, provide accurate information to the FDA and applicable foreign regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately and/or disclose unauthorized activities to us. In particular, research and development, sales, marketing and business arrangements in the healthcare industry are subject to considerable laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict, regulate or prohibit a wide range of activities pertaining to clinical trials including the informed consent process, data integrity and conducting the study in accordance with the investigational plan, and for approved products, pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other

business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions, possible exclusions from participation in Medicare, Medicaid and other U.S. federal healthcare programs, contractual damages and reputational harm.

If we or any contract manufacturers and suppliers we engage fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We and any contract manufacturers and suppliers we engage are subject to numerous federal, state and local environmental, health and safety laws, regulations and permitting requirements, including those governing laboratory procedures; the generation, handling, use, storage, treatment and disposal of hazardous and regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air and water; and employee health and safety. Under certain environmental laws, we could be held responsible for costs relating to any contamination at our current or past facilities and at third-party facilities. We also could incur significant costs associated with civil or criminal fines and penalties.

We could be adversely affected by violations of the U.S. Foreign Corrupt Practices Act, or the FCPA, and other worldwide anti-bribery laws.

We are subject to the FCPA, which prohibits U.S. corporations and their representatives from offering, promising, authorizing or making payments to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business abroad. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Other countries have enacted similar anti-corruption laws and/or regulations. In some countries in which we operate, the pharmaceutical and life sciences industries are exposed to a high risk of corruption associated with the conduct of clinical trials and other interactions with healthcare professionals and institutions. Any such activities could expose us to potential liability under the FCPA, which may result in us incurring significant criminal and civil penalties and to potential liability under the anti-corruption laws and regulations of other jurisdictions in which we operate. In addition, the costs we may incur in defending against an FCPA investigation could be significant.

Risks Related to the Separation and the Private Placement

We may not achieve some or all of the expected benefits of the separation, and the separation could harm our business, prospects, financial condition and results of operations.

We may not be able to achieve some or all of the anticipated strategic, financial, operational, marketing or other benefits expected to result from the separation, or such benefits may be delayed or not occur at all. These actions may not provide the benefits we currently expect, and could lead to disruption of our operations, loss of or inability to recruit, key personnel needed to operate and grow our businesses, weakening of our internal standards, controls or procedures and impairment of our key collaborations and supplier relationships.

By separating from Ironwood, we may become more susceptible to market fluctuations and other adverse events than we would have been if we were still a part of the Ironwood organizational

structure. As part of Ironwood, we were able to benefit from Ironwood's experience and expertise as a commercial-stage company developing multiple products, and opportunities to pursue integrated strategies with Ironwood's other business activities. We also benefited from Ironwood's strategic advantages as an established market participant, including its improved negotiating power and historical partnerships. Additionally, when we were part of Ironwood, we benefited from Ironwood's market reputation, historical performance and brand identity when operating our business. As a newly formed, independent, publicly traded company, we do not have, and may never develop, a comparable market reputation, performance or brand identity of our own, which may limit our ability to recruit and retain personnel, pursue and negotiate strategic transactions, and access the capital markets to finance our operations. If we fail to achieve some or all of the benefits that we expect to achieve as an independent company, or do not achieve them in the time we expect, our business, prospects, financial condition and results of operations may be materially harmed.

We may be unable to make, on a timely or cost-effective basis, the changes necessary to operate as an independent company, and we will be reliant on Ironwood for a period of time.

We have historically operated as part of Ironwood's corporate organization, and Ironwood has assisted us by providing various corporate and other business functions. As a result of the separation, Ironwood has no obligation to assist our operations or growth strategy, other than providing certain services or rights pursuant to agreements described under "Certain Relationships and Related Person Transactions—Agreements with Ironwood."

We are and for a period of time will be, substantially reliant on Ironwood to provide these limited services, and if Ironwood is unable or unwilling to satisfy its obligations under these agreements, we could incur operational difficulties or losses that could have a material and adverse effect on our business, prospects, financial condition and results of operations.

Furthermore, the services provided by Ironwood under these agreements do not include every service or all of the information and technology systems that we have received from Ironwood in the past or that are necessary to successfully operate our business, and Ironwood is only obligated to provide these services for limited periods of time. Accordingly, we must develop internal capabilities to perform these services, or obtain from other third parties services we currently receive from Ironwood. If we are unable to efficiently implement our own systems and services, or if we are unable to negotiate agreements with third-party providers of these services in a timely manner or on terms and conditions as favorable as those we receive from Ironwood, we may not be able to operate our business effectively and our financial condition may decline. Furthermore, if we fail to develop high-quality internal capabilities, or obtain comparable services from third-party providers, in a cost-effective manner, we may be unable to operate our existing business or execute our strategic priorities successfully and efficiently, and our operating results and financial condition may be materially harmed.

In addition, we entered into an intellectual property license agreement with Ironwood pursuant to which, in part, Ironwood granted to us a license to use certain Ironwood know-how in connection with our research and development of sGC stimulator products. If we were to use such licensed know-how and if our rights under the intellectual property license agreement were challenged by a third party or we were otherwise prevented from exercising our rights as contemplated under the intellectual property license agreement, our research and development activities could be delayed until we were able to either resume exercising such rights or develop or acquire adequate alternative know-how.

We have no history of operating as an independent company and we expect to incur increased administrative and other costs by virtue of our status as an independent public company. Our historical and pro forma financial information is not necessarily representative of the results that we would have achieved as a separate, publicly traded company and should not be relied upon as an indicator of our future results.

Our historical information provided in this prospectus refers to our business as operated by and integrated with Ironwood. Our historical and pro forma financial information included in this prospectus is derived from the consolidated financial statements and accounting records of Ironwood. Accordingly, the historical and pro forma financial information included in this prospectus may not reflect the operating results, financial condition or cash flows that we would have achieved as a separate, publicly traded company during the periods presented, or the financial results we will achieve in the future. In particular, our future financial results may vary from the historical and pro forma financial information included in this prospectus as a result of the following factors, among others:

- our historical combined financial data does not reflect the separation;
- our historical financial data reflects expense allocations for certain business and support functions that are provided on a centralized basis within Ironwood, such as expenses for research and development and corporate administrative services, including information technology, finance, legal, insurance, compliance and human resources activities, that may be lower than the comparable expenses we would have actually incurred, or will incur in the future, as a standalone company;
- our capital structure will be different from that reflected in our historical combined financial statements;
- significant increases may occur in our cost structure as a result of becoming a standalone public company, including costs related to public company reporting, investor relations and compliance with the Sarbanes-Oxley Act; and
- the separation may have a material effect on our relationships with our suppliers, collaborators and other business relationships.

Our financial condition and future results of operations, after giving effect to the separation, will be materially different from amounts reflected in our historical financial statements included elsewhere in this prospectus. As a result of the separation, it may be difficult for investors to compare our future results to historical results or to evaluate our relative performance or trends in our business.

The separation may impede our ability to attract and retain key personnel, which could materially harm our business.

Our success depends in large part upon the leadership and performance of our management team and other key employees. Operating as an independent company will demand a significant amount of time and effort from our management and other employees and may give rise to increased employee turnover. If we lose the services of members of our management team or other key employees, we may not be able to successfully manage our business or achieve our business objectives.

Our ability to attract, recruit and retain qualified key personnel in a highly competitive environment will depend on a number of factors, including the hiring practices of our competitors, the performance of our development programs, our compensation and benefits, work location and work environment and economic conditions affecting our industry generally. If we cannot effectively hire and retain qualified employees, our business, prospects, financial condition and results of operations could suffer.

Operating as an independent company may result in disruptions to, and harm our relationships with, our strategic business partners.

As we begin our operations as an independent company, the suppliers, research organizations, and other parties with which we currently do business or may do business in the future may terminate or attempt to negotiate changes in our existing business relationships, or delay entering into business relationships with us or consider entering into business relationships with parties other than us. These disruptions could have a material and adverse effect on our business, prospects, financial condition and results of operations.

If the distribution, together with certain related transactions, does not qualify as a transaction that is tax-free for U.S. federal income tax purposes, Ironwood and its stockholders could be subject to significant tax liabilities, and we could be required to indemnify Ironwood for material taxes pursuant to indemnification obligations under the tax matters agreement.

Ironwood has received a favorable private letter ruling from the IRS relating to the U.S. federal income tax treatment of the distribution. Consistent with the IRS's ruling guidelines, the IRS private letter ruling does not cover all of the issues that are relevant to determining whether the distribution is generally tax free for U.S. federal income tax purposes, including whether the distribution (i) satisfies the business purpose requirement in Section 1.355-2(b) of the Treasury Regulations, (ii) is used principally as a device for the distribution of our earnings and profits or the earnings and profits of Ironwood or both or (iii) is part of a plan (or series of related transactions) pursuant to which one or more persons will acquire directly or indirectly stock representing a 50% or greater interest in Ironwood or us. Accordingly, as a condition to the distribution, Ironwood received an opinion of KPMG LLP, satisfactory to Ironwood's board of directors, confirming that the distribution, together with certain related transactions, generally is tax-free for U.S. federal income tax purposes under Sections 355 and 368(a)(1)(D) of the Code. The opinion of KPMG LLP delivered to Ironwood and the IRS private letter ruling are based, among other things, on various facts and assumptions, as well as certain representations, statements and undertakings from us and Ironwood (including those relating to the past and future conduct of us and Ironwood). If any of these facts, assumptions, representations, statements or undertakings is, or becomes, inaccurate or incomplete, or if we or Ironwood breach any of our respective covenants relating to the separation, the IRS private letter ruling and/or the opinion of KPMG LLP may be invalid. Accordingly, notwithstanding receipt of the favorable IRS private letter ruling and the opinion of KPMG LLP delivered to Ironwood, the IRS could determine that the distribution and certain related transactions should be treated as taxable transactions for U.S. federal income tax purposes if it determines that any of the facts, assumptions, representations, statements or undertakings that were included in the request for the IRS private letter ruling or on which the opinion of KPMG LLP was based is inaccurate or incomplete or has been violated. In addition, the opinion of KPMG LLP delivered to Ironwood represents the judgment of KPMG LLP, which is not binding on the IRS or any court. Accordingly, notwithstanding receipt by Ironwood of the tax opinion and the favorable IRS private letter ruling referred to above, the IRS could assert that the distribution and/or certain related transactions do not qualify for tax-free treatment for U.S. federal income tax purposes.

If the distribution, together with certain related transactions, fails to qualify as a transaction that is tax-free under Sections 355 and 368(a)(1)(D) of the Code, for U.S. federal income tax purposes, Ironwood would recognize taxable gain with respect to our distributed common stock and Ironwood stockholders who received shares of our common stock in the distribution would be subject to tax as if they had received a taxable distribution equal to the fair market value of such shares.

Even if the distribution were otherwise to qualify as tax-free, for U.S. federal income tax purposes, under Sections 355 and 368(a)(1)(D) of the Code, it may result in taxable gain to Ironwood under Section 355(e) of the Code if the distribution were deemed to be part of a plan (or series of related transactions) pursuant to which one or more persons acquire, directly or indirectly, shares representing

a 50% or greater interest (by vote or value) in Ironwood or us. Under the terms of the common stock purchase agreement, the investors in the private placement acquired 43% of our common stock on a basic shares outstanding method. For purposes of this test, the private placement will generally be treated as part of such a plan or series of transactions, although some portion of the private placement may be excluded from such treatment if investors who owned shares of Ironwood common stock immediately prior to the distribution participate in the private placement to maintain their respective ownership held immediately prior to the private placement. Nonetheless, the rules governing such exclusions are complex, and there can be no assurance given as to the amount or percentage of the private placement that will be excluded from such treatment under these rules. Thus, a relatively minor additional change in the ownership of the our common stock (or, prior to the distribution, in the Ironwood common stock) could trigger a prohibited change in control, resulting in a significant amount of taxable gain for Ironwood under Section 355 of the Code (as a result of which we would be required to indemnify Ironwood under the tax matters agreement, as discussed below), if that additional ownership change and the portion of the private placement that must be taken into account were each considered to be part of a plan or series of related transactions that included the distribution and, in the aggregate, resulted in a 50% or greater change in ownership of our common stock, as determined under the Code and applicable Treasury regulations. The process for determining whether a prohibited change in control has occurred under the rules is complex, inherently factual and subject to interpretation of the facts and circumstances of a particular case. If we or Ironwood do not carefully monitor our or its compliance with these rules, we or Ironwood might inadvertently cause or permit a prohibited change in our ownership or the ownership of Ironwood. Furthermore, sales and/or acquisitions by the investors in the private placement (or by other persons) of our or Ironwood common stock after completion of the distribution could potentially trigger a prohibited change of control in us or Ironwood. For purposes of these rules, any acquisitions of Ironwood or our shares within the period beginning two years before the distribution and ending two years after the distribution are presumed to be part of such a plan, although we or Ironwood may be able to rebut that presumption based on the facts or circumstances or under regulatory safe harbors.

In connection with the distribution, we entered into a tax matters agreement with Ironwood pursuant to which we are responsible for certain liabilities and obligations following the distribution. In general, under the terms of the tax matters agreement, if the distribution, together with certain related transactions, were to fail to qualify as a transaction that is generally tax-free, for U.S. federal income tax purposes, under Sections 355 and 368(a)(1)(D) of the Code, and if and to the extent that such failure results from a prohibited change of control in Ironwood under Section 355(e) of the Code or an acquisition of shares of Ironwood common stock or assets or certain actions by Ironwood, then Ironwood will bear any resulting taxes, interest, penalties and other costs. If and to the extent that such failure results from a prohibited change of control in us under Section 355(e) of the Code or an acquisition of our stock or assets or certain actions by us, then we will indemnify Ironwood for any resulting taxes, interest, penalties and other costs, including any reductions in Ironwood's net operating loss carryforwards or other tax assets. If such failure does not result from a prohibited change of control in Ironwood or us under Section 355(e) of the Code and both we and Ironwood are responsible for such failure, liability will be shared according to relative fault. If neither we nor Ironwood is responsible for such failure, Ironwood will bear any resulting taxes, interest, penalties and other costs. For a discussion of the tax matters agreement, see "Certain Relationships and Related Person Transactions—Agreements with Ironwood—Tax Matters Agreement." Our indemnification obligations to Ironwood under the tax matters agreement are not expected to be limited in amount or subject to any cap. If we are required to pay any taxes or indemnify Ironwood and its subsidiaries and their respective officers and directors under the circumstances set forth in the tax matters agreement, we may be subject to substantial liabilities.

We may not be able to engage in attractive strategic or capital-raising transactions following the separation.

To preserve the tax-free treatment of the separation and the distribution for U.S. federal income tax purposes, for the two-year period before and ending two years after the distribution, we will be prohibited under the tax matters agreement, except in specific circumstances, from: (i) entering into or approving any transaction involving the acquisition of our outstanding or newly issued equity that, when combined with other changes in ownership of our capital stock, results in a change in ownership of 3% or more; (ii) liquidating or partially liquidating, or merging or consolidating (unless we are the survivor); (iii) making or changing any entity classification election; (iv) ceasing to be engaged in an active trade or business, or selling, transferring or disposing of 25% or more of the net or gross assets of any active trade or business; (v) amending any of our organizational documents or taking any action affecting the voting rights of our capital stock; (vi) redeeming or otherwise repurchasing any of our outstanding stock or options; or (vii) taking or failing to take any other action that would prevent the distribution and certain related transactions from qualifying as a transaction that is generally tax-free for U.S. federal income tax purposes under Sections 355 and 368(a)(1) (D) of the Code. These restrictions may limit for a period of time our ability to pursue certain strategic transactions, equity issuances or repurchases or other transactions that we may believe to be in the best interests of our shareholders or that might increase the value of our business. For more information, see "Certain Relationships and Related Person Transactions—Agreements with Ironwood—Tax Matters Agreement."

In connection with the separation, we assumed and agreed to indemnify Ironwood for certain liabilities. If we are required to make payments pursuant to these indemnities to Ironwood, we may need to divert cash to meet those obligations and our financial results could be harmed.

Pursuant to the separation agreement and certain other agreements we entered into with Ironwood, we assumed and agreed to indemnify Ironwood for certain liabilities for uncapped amounts, which may include, among other items, associated defense costs, settlement amounts and judgments, as discussed further in "Certain Relationships and Related Person Transactions—Agreements with Ironwood" and "Index to Financial Statements—Audited Combined Financial Statements—Notes to Combined Financial Statements." Payments pursuant to these indemnities may be significant and could harm our business, particularly indemnities relating to our actions that could impact the tax-free nature of the distribution and certain related transactions. Third parties could also seek to hold us responsible for any of the liabilities of the Ironwood business. Ironwood agreed to indemnify us for liabilities of the Ironwood business, but such indemnity from Ironwood may not be sufficient to protect us against the full amount of such liabilities, and Ironwood may not fully satisfy its indemnification obligations. Moreover, even if we ultimately succeed in recovering from Ironwood any amounts for which we are held liable, we may be temporarily required to bear these losses ourselves. Each of these risks could harm our business, prospects, financial condition and results of operations.

Our agreements with Ironwood may not reflect terms that would have resulted from negotiations with unaffiliated third parties.

The agreements related to the separation, including, among others, the separation agreement, the employment matters agreement, the tax matters agreement, the intellectual property license agreement, the transition services agreements and the development agreement, were negotiated in the context of the separation while we were still controlled by Ironwood. Until the distribution occurred, Ironwood effectively had the sole and absolute discretion to determine and change the terms of the separation, including the terms of any agreements between Ironwood and us and the establishment of the record date and distribution date. As a result, any changes could be unfavorable to us and may not reflect terms that would have resulted from negotiations between unaffiliated third parties. For a more detailed description, see "Certain Relationships and Related Person Transactions—Agreements with Ironwood."

Certain of our directors and officers may have actual or potential conflicts of interest because of their former positions with Ironwood.

Certain of our directors and officers may own shares of Ironwood common stock or other equity awards as a result of their prior service as Ironwood directors or officers. For certain of these individuals, their holdings of Ironwood common stock or equity awards may be significant compared to their total assets. The ownership of any Ironwood equity or equity awards creates, or may create the appearance of, conflicts of interest when these directors or officers are faced with decisions that could have different implications for Ironwood than for us. Potential conflicts or the appearance of conflicts may also arise because Mark Currie, our President, also serves as a director on Ironwood's board of directors. These potential conflicts could arise, for example, over matters such as the desirability of changes in our business and operations, funding and capital matters, regulatory matters, matters arising with respect to the separation agreement and other agreements with Ironwood relating to the separation or otherwise, employee retention or recruiting, or our dividend policy.

The trading price of our common stock may not reflect the full value of our business and assets.

The trading price of our common stock may not reflect the full value of our business and assets, due to market inefficiencies in the initial trading of our shares or variations in investor views regarding our business and prospects, among other market forces. The aggregate market value of our common stock may fluctuate, particularly during the period following the distribution.

Risks Related to Ownership of Our Common Stock

An active trading market may not develop for our shares and the market price of these shares may fluctuate widely.

Prior to the first trading day following the distribution, there had been no public market for our shares of common stock. Although our common stock has been approved for listing on Nasdaq, there can be no assurance that an active trading market for our shares of common stock will develop or be sustained in the future.

We cannot predict the prices at which our shares of common stock may trade. The market price of our shares of common stock may fluctuate widely, depending upon many factors, some of which are beyond our control, including the following:

- a relatively low-volume trading market for our shares of common stock may result, which could cause trades of small blocks of shares to have a significant impact on the price of our shares of common stock;
- results and timing of preclinical studies and clinical studies of our product candidates;
- the commercial performance of our products, if approved, as well as the costs associated with such activities;
- results of clinical studies of our competitors' products;
- failure to adequately protect our trade secrets;
- our inability to raise additional capital and the terms on which we raise it;
- commencement or termination of any strategic partnership or licensing arrangement;
- regulatory developments with respect to our products or our competitors' products, including any developments, litigation or public concern about the safety of such products;
- announcements concerning product development results, including clinical trial results, the introduction of new products or intellectual property rights of us or others;

- actual or anticipated fluctuations in our financial condition and our quarterly and annual operating results;
- deviations in our operating results from any guidance we may provide or the estimates of securities analysts;
- additions and departures of key personnel;
- the passage of legislation or other regulatory developments affecting us or our industry;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other shareholders;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- announcement or expectation of additional financing efforts;
- publication of research reports by securities analysts about us or our competitors or our industry and speculation regarding our company or our stock price in the financial or scientific press or in online investor communities;
- changes in market conditions in the pharmaceutical and biotechnology sector; and
- changes in general market and economic conditions.

In addition, if the market for stocks in our industry or industries related to our industry, or the stock market in general, experiences a loss of investor confidence, the trading price of our common stock could decline for reasons unrelated to our business, results of operations, financial condition and prospects. If any of the foregoing occurs, it could cause our stock price to fall and may expose us to lawsuits that, even if unsuccessful, could be costly to defend and a distraction to management.

Substantial sales of shares of our common stock may occur in the immediate future, which could cause the market price of shares of our common stock to decline.

It is possible that many of our shareholders who received their shares in the distribution or purchased their shares in the private placement will sell their shares of our common stock in the public market because our business profile or market capitalization does not fit their investment objectives, because the shares are not included in certain indices or for other reasons. The sale of significant amounts of our shares or the perception in the market that this will occur may result in the lowering of the market price of our shares. We can offer no assurance that our shareholders will continue to hold the shares they received in the distribution.

If securities or industry analysts fail to initiate or maintain coverage of our stock, publish a negative report or change their recommendations regarding our stock adversely, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us, our business, our market or our competitors. If securities or industry analysts fail to initiate coverage of our stock, the lack of exposure to the market could cause our stock price or trading volume to decline. If any of the analysts who cover us or may cover us in the future publish a negative report or change their recommendation regarding our stock adversely, or provide more favorable relative recommendations about our competitors, our stock price would likely decline. If any analyst who covers us or may cover us in the future were to cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Your percentage ownership in the company may be diluted in the future.

In the future, your percentage ownership in the company may be diluted because of equity issuances for acquisitions, capital market transactions or otherwise, including equity awards that we plan to grant to our directors, officers and employees. Such awards will have a dilutive effect on our earnings per share, which could adversely affect the market price of our common stock. From time to time, we expect to issue stock options or other share-based awards to employees under our employee benefits plans.

In addition, our articles of organization will authorize us to issue, without the approval of our shareholders, one or more classes or series of preferred stock having such designation, powers, preferences and relative, participating, optional and other special rights, including preferences over our common stock with respect to dividends and distributions, as our board of directors may determine. The terms of one or more classes or series of preferred stock could dilute the voting power or reduce the value of our common stock. For example, we could grant the holders of preferred stock the right to elect some number of directors in all events or on the happening of specified events or the right to veto specified transactions. Similarly, the repurchase or redemption rights or liquidation preferences we could assign to holders of preferred stock could affect the residual value of the common stock. See "Description of Cyclerion's Capital Stock."

We do not expect to pay any cash dividends for the foreseeable future.

We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. In addition, any future debt financing arrangement may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

We have adopted anti-takeover provisions in our articles of organization and bylaws and are subject to provisions of Massachusetts law that may frustrate any attempt to remove or replace our current board of directors or to effect a change of control or other business combination involving our company.

Our articles of organization and bylaws and certain provisions of Massachusetts law may discourage certain types of transactions involving an actual or potential change of control of our company that might be beneficial to us or our security holders. For example, our bylaws grant our directors the right to adjourn any meetings of shareholders. Our board of directors also may issue shares of any class or series of preferred stock in the future without shareholder approval and upon such terms as our board of directors may determine. The rights of the holders of our common stock will be subject to, and may be harmed by, the rights of the holders of any class or series of preferred stock that may be issued in the future. Massachusetts state law also prohibits us from engaging in specified business combinations unless the combination is approved or consummated in a prescribed manner. These provisions, alone or together, could delay hostile takeovers and changes in control of our company or changes in our management.

Our articles of organization designate the state and federal courts located within the Commonwealth of Massachusetts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our shareholders, which could discourage lawsuits against us and our directors and officers.

Our articles of organization designate the state and federal courts located within the Commonwealth of Massachusetts as the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by

any of our directors or officers to us or our shareholders, creditors or other constituents, any action asserting a claim arising pursuant to any provision of the Massachusetts Business Corporation Act, or the MBCA, or any action asserting a claim governed by the internal affairs doctrine, in all cases subject to the court's having personal jurisdiction over the indispensable parties named as defendants. In additional, our articles of organization provide that unless our board of directors consents in writing to the selection of an alternative forum, the U.S. federal district courts shall be the exclusive forum for the resolutions of any complaint asserting a cause of action arising under the U.S. federal securities laws. This exclusive forum provision may limit the ability of our shareholders to bring a claim in a judicial forum that such shareholders find favorable for disputes with us or our directors or officers, which may discourage such lawsuits against the company and our directors and officers. Alternatively, if a court outside of Massachusetts were to find this exclusive forum provision inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings described above, we may incur additional costs associated with resolving such matters in other jurisdictions, which could harm our business, prospects, financial condition and results of operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY AND MARKET DATA

This prospectus and other materials we have filed or will file with the SEC include, or will include, forward-looking statements. All statements in this prospectus, in other materials we have filed or will file with the SEC and in related comments by our management, other than statements of historical facts, including statements about future events, financing plans, financial position, business strategy, budgets, projected costs, plans and objectives of management for future operations, are forward-looking statements that involve certain risks and uncertainties. Use of the words "may," "will," "would," "could," "should," "believes," "estimates," "projects," "potential," "expects," "plans," "seeks," "intends," "evaluates," "pursues," "anticipates," "continues," "designs," "impacts," "affects," "forecasts," "target," "outlook," "initiative," "objective," "designed," "priorities," "goal" or the negative of those words or other similar expressions may identify forward-looking statements that represent our current judgment about possible future events, but the absence of these words does not necessarily mean that a statement is not forward-looking.

Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward-looking statements relate to the future, by their nature, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. As a result, our actual results may differ materially from those contemplated by the forward-looking statements. Important factors that could cause actual results to differ materially from those in the forward-looking statements include regional, national or global political, economic, business, competitive, market and regulatory conditions and the following:

- our business and operations following the separation and any benefits or costs of the separation, including the tax treatment;
- our post-separation relationships with Ironwood, third parties, collaborators and our employees;
- our ability to operate as a standalone company and execute our strategic priorities;
- our ability to finance our operations and business initiatives and obtain funding for such activities;
- the timing, investment and associated activities involved in developing, obtaining regulatory approval for, launching and commercializing our product candidates, including olinciguat, praliciguat and IW-6463;
- our plans with respect to the development, manufacture or sale of our product candidates and the associated timing thereof, including the design and results of pre-clinical and clinical studies;
- the safety profile and related adverse events of our product candidates;
- the efficacy and perceived therapeutic benefits of our product candidates and the potential indications and market opportunities therefor;
- U.S. and foreign regulatory requirements for our product candidates, including any post-approval development and regulatory requirements, and the ability of our product candidates to meet such requirements;
- our ability to attract and retain key employees needed to execute our business plans and strategies and our expectations regarding our ability to manage the impact of any loss of key employees;
- our ability to obtain and maintain intellectual property protection for our product candidates and the strength thereof;

- our future financial performance, revenues, expense levels, payments, cash flows, profitability, tax obligations, capital raising and liquidity sources, real estate needs and concentration of voting control, as well as the timing and drivers thereof, and internal control over financial reporting;
- our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates;
- the status of government regulation in the life sciences industry, particularly with respect to healthcare reform;
- potential indemnification liabilities we may owe to Ironwood after the separation;
- the tax treatment of the distribution and the limitations imposed on us under the tax matters agreement that we entered into with Ironwood; and
- trends and challenges in our potential markets.

See "Risk Factors" for a further description of these and other factors. Although we have attempted to identify important risk factors, there may be other risk factors not presently known to us or that we presently believe are not material that could cause actual results and developments to differ materially from those made in or suggested by the forward-looking statements contained in this prospectus. If any of these risks materialize, or if any of the assumptions underlying forward-looking statements prove incorrect, actual results and developments may differ materially from those made in or suggested by the forward-looking statements contained in this prospectus. For the reasons described above, we caution you against relying on any forward-looking statements, which should also be read in conjunction with the other cautionary statements that are included elsewhere in this prospectus. Any forward-looking statement made by us in this prospectus speaks only as of the date thereof. Factors or events that could cause our actual results to differ may emerge from time to time, and it is not possible for us to predict all of them. We undertake no obligation to publicly update or to revise any forward-looking statement, whether as a result of new information, future developments, or otherwise, except as may be required by law.

USE OF PROCEEDS

All shares of our common stock sold pursuant to this prospectus will be offered and sold by the selling stockholders. We will not receive any proceeds from such sales.

DIVIDEND POLICY

We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects and any other factors deemed relevant by our board of directors.

UNAUDITED PRO FORMA COMBINED FINANCIAL STATEMENTS

Our unaudited pro forma combined financial data consists of an unaudited pro forma combined statement of income for the year ended December 31, 2018 and an unaudited pro forma combined balance sheet as of December 31, 2018 prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP. The unaudited pro forma combined financial data reported below should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations," "Summary Historical and Unaudited Pro Forma Combined Financial Information" and the audited and unaudited combined financial statements and corresponding notes included elsewhere in this prospectus.

The following unaudited pro forma combined financial data is subject to assumptions and adjustments described in the accompanying notes. Our management believes these assumptions and adjustments are reasonable under the circumstances and given the information available at this time. The unaudited pro forma combined financial data does not purport to represent what our financial position and results of operations actually would have been had the separation occurred on the dates indicated, or to project our financial performance for any future period following the separation.

The unaudited pro forma combined financial data as of and for the year ended December 31, 2018 gives effect to the separation as if it had occurred on January 1, 2018. The unaudited pro forma combined financial data includes adjustments to reflect the following:

- the contribution by Ironwood to us, pursuant to the separation agreement, of all the assets and liabilities that comprise our business;
- the transfer certain assets and liabilities that were not included in our historical combined financial statements;
- the impact of the separation agreement, tax matters agreement, employee matters agreement, development agreement, intellectual property license agreement, transition services agreements and other commercial agreements between us and Ironwood;
- the receipt of $165.0 million net proceeds from the issuance and sale of 11,817,165 shares of our common stock in the private placement pursuant to the terms of the purchase agreement;
- the impact of the execution of our building lease agreement, including a letter of credit posted with the landlord as a security deposit; and
- the impact of the execution of our directors and officers, management liability, and property and casualty insurance policies.

Our historical financial information, which was the basis for the unaudited pro forma combined financial statements, was prepared on a carve-out basis as we were not operated as a separate, independent company for the periods presented. Accordingly, such historical financial information reflects an allocation for certain business and support functions that are provided on a centralized basis within Ironwood, such as expenses for research and development and corporate administrative services, including information technology, finance, legal, insurance, compliance and human resources activities. These historical allocations may not be indicative of our future cost structure; however, the pro forma results have not been adjusted to reflect any potential changes associated with being an independent public company as such amounts are estimates that are not factually supportable.

Ironwood incurred approximately $22.9 million of one-time separation costs in connection with the separation during 2018, including costs related to consulting, legal, auditing and information technology, of which $8.0 million was allocated to us. In connection with the completion of the distribution on April 1, 2019 and the closing of the private placement on April 2, 2019, we incurred one-time transaction costs of approximately $10.0 million.

Cyclerion Therapeutics, Inc.
Unaudited Pro Forma Combined Statement of Operations
Year Ended December 31, 2018
(in thousands)

	Historical	Pro forma Adjustments	Notes	Adjusted
Cost and expenses:			[A, B]	
Research and development	$ 87,716			$ 87,716
General and administrative	27,536	8,233	[A, F, G]	35,769
Total cost and expenses	115,252			123,485
Loss from operations	(115,252)			(123,485)
Net loss	$ (115,252)			$ (123,485)
Unaudited Pro Forma Earnings Per Share				
Basic and Diluted	N/A		[C, D]	$ (4.51)
Average Number of Shares Used in Calculating				
Basic and Diluted	N/A		[C, D]	27,402

See Notes to Unaudited Pro forma Combined Financial Data

Cyclerion Therapeutics, Inc.
Unaudited Pro Forma Combined Balance Sheet
As of December 31, 2018
(in thousands)

	Historical	Pro forma Adjustments	Notes	Adjusted
ASSETS			[A]	
Current assets:				
Cash and cash equivalents	$ —	149,296	[E, F, G]	$ 149,296
Prepaid expenses	867			867
Other current assets	12			12
Total current assets	879			150,175
Restricted Cash	—	7,726	[H]	7,726
Property and equipment, net	6,497	3,459	[A]	9,956
Other assets	25			25
Total assets	$ 7,401			$ 167,882
Current liabilities:			[A, B]	
Accounts payable	$ 2,781	(2,781)	[A]	$ —
Accrued research and development costs	5,261			5,261
Accrued expenses and other current liabilities	9,804	1,300	[I]	11,104
Total current liabilities	17,846			16,365
Equity:				
Common Stock	N/A			
Additional paid-in capital	N/A	151,517	[C, E]	151,517
Net parent investment	(10,445)	10,445	[A]	—
	(10,445)			151,517
Total liabilities and equity	$ 7,401			$ 167,882

See Notes to Unaudited Pro forma Combined Financial Data

Cyclerion Therapeutics, Inc.

Notes to Unaudited Pro Forma Combined Balance Sheet
As of December 31, 2018

(A) Reflects the impact of assets, liabilities and related expenses that we assumed from Ironwood that were not included in our unaudited combined financial statements. We assumed approximately $3.5 million of property, plant and equipment, net, primarily related to the assumption of a portion of Ironwood's former headquarters and accounts payable of $2.8 million did not transfer to us from Ironwood, which resulted in a net increase in net parent investment. Depreciation expense associated with the transferred property, plant and equipment, net was $0.3 million for the year ended December 31, 2018.

(B) Reflects the tax effects of the pro forma adjustments at the applicable effective income tax rate of zero for the year ended December 31, 2018. Our effective tax rate could be different (either higher or lower) depending on activities subsequent to the separation. The impact of pro forma adjustments on long-term deferred tax assets and liabilities were offset against existing long-term deferred tax assets and liabilities reflected in our historical combined balance sheet, all of which are offset by valuation allowance in full.

(C) The number of shares of our common stock used to compute basic earnings per share is based on: (a) the number of shares of our common stock outstanding on the distribution date, after giving effect to the distribution, calculated based on 155,625,549 shares of Ironwood common stock outstanding on March 29, 2019, and a distribution ratio of one share of our common stock for every 10 shares of Ironwood common stock, and (b) the issuance of 11,817,165 shares of our common stock in the private placement.

(D) The number of shares used to compute diluted earnings per share is based on the number of shares of our common stock as described in Note (C) above, plus incremental shares assuming exercise of dilutive options and restricted stock awards issued in connection with the separation. This calculation may not be indicative of the dilutive effect that will actually result from our share-based awards issued in connection with the adjustment of outstanding Ironwood share-based awards or the grant of new share-based awards. The number of dilutive shares of common stock underlying our share-based awards issued in connection with the adjustment of outstanding Ironwood share-based awards is 7,389,451.

(E) Reflects cash proceeds from the issuance and sale of shares of our common stock in the private placement pursuant to the terms of the purchase agreement, after the payment of certain finance-related expenses.

(F) Reflects the increase of $7.3 million in building lease related expenses based on a direct building lease of its existing operating premises, consisting of approximately 114,000 square feet of office and lab space.

(G) Reflects the increase of $0.6 million in directors and officers, management liability, and property and casualty insurance related expenses.

(H) Reflects the amount under a letter of credit posted with the landlord as a security deposit, related to our lease agreement, in the amount of approximately $7.7 million.

(I) Reflects the amount due to Ironwood related to tenant improvements that were paid for by Ironwood prior to separation and will be reimbursed to Cyclerion as part of the building lease agreement.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with "Unaudited Pro Forma Combined Financial Statements," "Summary Historical and Unaudited Pro Forma Combined Financial Information" and the audited and unaudited combined financial statements and corresponding notes included elsewhere in this prospectus. This discussion and analysis contains forward-looking statements that involve significant risks and uncertainties. As a result of many factors, including those set forth under "Risk Factors" appearing elsewhere in this prospectus, our actual results may differ materially from those anticipated in these forward-looking statements.

Overview

We are a clinical-stage biopharmaceutical company harnessing the power of sGC pharmacology to discover, develop and commercialize breakthrough treatments for serious and orphan diseases. Our focus is enabling the full therapeutic potential of next-generation sGC stimulators. Our strategy rests on a solid scientific foundation that is enabled by our people and capabilities, external collaborations and a responsive capital allocation approach.

We operate in one reportable business segment—human therapeutics.

Separation from Ironwood Pharmaceuticals

In May 2018, Ironwood announced its plans to separate its sGC business from its commercial and gastrointestinal business through a pro rata distribution of Cyclerion common stock to stockholders of Ironwood. Effective upon completion of the separation on April 1, 2019, Ironwood transferred the assets, liabilities and operations of its sGC stimulator and discovery research business to Cyclerion, pursuant to the terms of a separation agreement, entered into between Ironwood and Cyclerion. On April 1, 2019, each Ironwood stockholder received one share of Cyclerion's common stock for every 10 shares of Ironwood common stock held of record at the close of business on March 19, 2019. Registered stockholders received cash in lieu of any fractional shares of Cyclerion's common stock that they would have received as a result of the application of the distribution ratio. Following the completion of the separation, Cyclerion operates as a separate, independent, publicly traded company.

Our historical combined financial statements have been prepared on a stand-alone basis and are derived from Ironwood's combined financial statements and accounting records and are presented in conformity with U.S. GAAP. Our financial position, results of operations and cash flows historically operated as part of Ironwood's financial position, results of operations and cash flows prior to April 1, 2019. These historical combined financial statements may not be indicative of our future performance and do not necessarily reflect what our combined results of operations, financial condition and cash flows would have been had we operated as a separate, publicly traded company during the periods presented.

Financial Overview

Research and Development Expense. Research and development expense consists of expenses incurred in connection with the discovery and development of our product candidates. These expenses consist primarily of compensation, benefits and other employee-related expenses, research and development related facility costs, and third-party contract costs relating to nonclinical study and clinical trial activities. All research and development expenses are charged to operations as incurred.

The core of our research and development strategy is to harness the power of sGC pharmacology to develop therapies for serious and orphan diseases.

Olinciguat is an orally administered, once-daily, vascular sGC stimulator that is well suited for the potential treatment of SCD. We are conducting a Phase 2 study, STRONG-SCD, that is expected to enroll approximately 88 patients. During the periods presented, costs associated with olinciguat include clinical studies regarding achalasia.

In June 2018, the FDA granted Orphan Drug Designation to olinciguat for the treatment of patients with SCD. Orphan Drug Designation provides marketing exclusivity for seven years from the date of the product's approval for marketing, and contributes to a significant reduction in development costs.

Praliciguat is an orally administered, once-daily systemic sGC stimulator that is well suited for the potential treatment of serious cardiometabolic diseases given its very extensive distribution into tissues, particularly adipose, kidney, heart and liver. Praliciguat is currently in a dose-ranging Phase 2 study in approximately 150 adult patients with DN. Additionally, we initiated a clinical program in HFpEF. We are conducting a Phase 2 proof-of-concept trial, CAPACITY-HFpEF, in approximately 184 patients.

In September 2018, the FDA granted Fast Track Designation for praliciguat for the treatment of patients with HFpEF. A drug granted Fast Track Designation is eligible for several benefits, such as more frequent meetings with and communications from the FDA.

IW-6463 is an orally administered CNS-penetrant sGC stimulator that, because it readily crosses the blood-brain barrier, affords an unprecedented opportunity to expand the utility of sGC pharmacology to serious neurodegenerative diseases. In January 2019, we initiated our first-in-human study of IW-6463.

Discovery Research. Our discovery efforts are primarily focused on identifying, designing and developing sGC stimulators in serious and orphan diseases. sGC stimulation is a powerful mechanism that can broadly regulate blood flow, inflammation, fibrosis and metabolism. In diseases that are localized to specific organs or tissues, we believe that our organ-targeting strategy will maximize the efficacy of sGC pharmacology in key organs while reducing the potential for dose-limiting hemodynamic effects sometimes observed with sGC stimulation. Our initial focus is on the liver and the lung due to the clear role of nitric oxide signaling in diseases with high unmet need that affect these organs.

The following table sets forth our research and development expenses related to our product pipeline, as well as employee and facility related costs allocated to research and development expense, for the years ended December 31, 2017 and 2018. These product pipeline expenses relate primarily to external costs associated with nonclinical studies and clinical trial costs, which are presented by development candidates.

	Year Ended December 31,	
	2017	2018
Development candidates:		
Praliciguat	$ 18,807	$ 18,375
Olinciguat	5,254	6,901
IW-6463	2,421	2,653
Discovery research	2,642	2,635
Total development candidates	29,124	30,564
Personnel and related costs	30,056	35,707
Facilities and others	19,623	21,445
Total research and development expenses	$ 78,803	$ 87,716

The lengthy process of securing regulatory approvals for new drugs requires the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining regulatory approvals would materially adversely affect our product development efforts and our business overall.

Given the inherent uncertainties that come with the development of pharmaceutical products, we cannot estimate with any degree of certainty how our programs will evolve, and therefore the amount of time or money that will be required to obtain regulatory approval to market them. As a result of these uncertainties surrounding the timing and outcome of any approvals, we are currently unable to estimate precisely when, if ever, our discovery and development candidates will be approved.

We invest carefully in our pipeline, and the commitment of funding for each subsequent stage of our development programs is dependent upon the receipt of clear, supportive data.

The successful development of our product candidates is highly uncertain and subject to a number of risks including, but not limited to:

- The duration of clinical trials may vary substantially according to the type and complexity of the product candidate and may take longer than expected.
- The FDA and comparable agencies in foreign countries impose substantial and varying requirements on the introduction of therapeutic pharmaceutical products, which typically require lengthy and detailed laboratory and clinical testing procedures, sampling activities and other costly and time-consuming procedures.
- Data obtained from nonclinical and clinical activities at any step in the testing process may be adverse and lead to discontinuation or redirection of development activity. Data obtained from these activities also are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval.
- The duration and cost of discovery, nonclinical studies and clinical trials may vary significantly over the life of a product candidate and are difficult to predict.
- The costs, timing and outcome of regulatory review of a product candidate may not be favorable, and, even if approved, a product may face post-approval development and regulatory requirements.
- The emergence of competing technologies and products and other adverse market developments may negatively impact us.

As a result of the factors discussed above, including the factors discussed under the "Risk Factors" section of this prospectus, we are unable to determine the duration and costs to complete current or future nonclinical and clinical stages of our product candidates or when, or to what extent, we will generate revenues from the commercialization and sale of our product candidates. Development timelines, probability of success and development costs vary widely. We anticipate that we will make determinations as to which additional programs to pursue and how much funding to direct to each program on an ongoing basis in response to the data from the studies of each product candidate, the competitive landscape and ongoing assessments of such product candidate's commercial potential.

General and Administrative Expense. General and administrative expense consists primarily of compensation, benefits and other employee-related expenses for personnel in our administrative, finance, legal, information technology, business development, communications and human resource functions. Other costs include the legal costs of pursuing patent protection of our intellectual property, general and administrative related facility costs, insurance costs and professional fees for accounting and legal services. We record all general and administrative expenses as incurred.

Critical Accounting Policies and Estimates

Our discussion and analysis of our financial condition and results of operations is based upon our combined financial statements prepared in accordance with U.S. GAAP. The preparation of these financial statements requires us to make certain estimates and assumptions that may affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the combined financial statements, and the amounts of expenses during the reported periods. Significant estimates and assumptions in our combined financial statements include those related to allocations of expenses, assets and liabilities from Ironwood's historical financials; impairment of long-lived assets; income taxes, including the valuation allowance for deferred tax assets; research and development expenses; contingencies and share-based compensation. We base our estimates on our historical experience and on various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results may differ materially from our estimates under different assumptions or conditions. Changes in estimates are reflected in reported results in the period in which they become known.

We believe that our application of the accounting policy noted below requires significant judgments and estimates on the part of management, and is the most critical to aid in fully understanding and evaluating our reported financial results. Our significant accounting policies are more fully described in Note 2, *Summary of Significant Accounting Policies*, to our combined financial statements appearing elsewhere in this prospectus.

Research and Development Expense

All research and development expenses are expensed as incurred. We defer and capitalize nonrefundable advance payments we make for research and development activities until the related goods are received or the related services are performed. See Note 2, *Summary of Significant Accounting Policies*, of the combined financial statements appearing elsewhere in this prospectus.

Results of Operations

Historically, our operations have been managed in the normal course of business as part of Ironwood. Accordingly, certain shared costs have been allocated to us and reflected as expenses in the stand-alone combined financial statements, as described in greater detail in the notes to the combined financial statements appearing elsewhere in this prospectus. We considered the allocation methodologies used to be a reasonable and appropriate reflection of the historical Ironwood expenses attributable to us for purposes of the stand-alone financial statements. The expenses reflected in the combined financial statements may not be indicative of expenses that will be incurred by us in the future. The following discussion summarizes the key factors we believed are necessary for an understanding of our combined financial statements.

Years ended December 31, 2016 compared to December 31, 2017

	Year Ended December 31,			
	2016	2017	Change	
	(in thousands)		$	%
Cost and expenses:				
Research and development	$ 50,903	$ 78,803	$ 27,900	55%
General and administrative	12,651	15,119	2,468	20%
Total cost and expenses	63,554	93,922	$ 30,368	48%
Loss from operations	(63,554)	(93,922)		
Net loss	$ (63,554)	$ (93,922)		

Research and Development Expense. The increase in research and development expense of approximately $27.9 million for the year ended December 31, 2017 compared to the year ended December 31, 2016 was primarily related to an increase of approximately $15.5 million in external research costs associated with clinical advancements for our product candidates, including costs associated with two Phase 2a studies of praliciguat; an increase of approximately $9.6 million in compensation, benefits and other employee-related expenses primarily associated with increased headcount; and an increase of approximately $1.8 million in operating costs, including facilities, allocated to research and development.

General and Administrative Expense. General and administrative expenses increased approximately $2.5 million for the year ended December 31, 2017 compared to the year ended December 31, 2016 primarily as a result of an increase in $1.4 million in compensation, benefits and other employee-related expenses and an increase of approximately $1.0 million in external consulting costs, recruiting costs and other professional service costs; offset by a decrease of approximately $0.2 million in costs related to facilities and information technology infrastructure.

Years ended December 31, 2017 compared to December 31, 2018

	Year Ended December 31,			
	2017	2018	Change	
	(in thousands)		$	%
Cost and expenses:				
Research and development	$ 78,803	$ 87,716	$ 8,913	11%
General and administrative	15,119	27,536	12,417	82%
Total cost and expenses	93,922	115,252	$ 21,330	23%
Loss from operations	(93,922)	(115,252)		
Net loss	$ (93,922)	$ (115,252)		

Research and Development Expense. The increase in research and development expense of approximately $8.9 million for the year ended December 31, 2018 compared to the year ended December 31, 2017 was primarily related to an increase of approximately $3.5 million in compensation, benefits and other employee-related expenses; an increase of approximately $2.6 million in operating costs, including facilities, allocated to research and development, an increase of approximately $2.0 million related to workforce reduction charges associated with the initial organizational designs for the continuing Ironwood and Cyclerion businesses and an increase of approximately $0.3 million in external research costs associated with clinical advancements for our product candidates, including costs associated with initiation of STRONG-SCD, a Phase 2 clinical trial for olinciguat.

General and Administrative Expense. General and administrative expenses increased approximately $12.4 million for the year ended December 31, 2018 compared to the year ended December 31, 2017 primarily as a result of an increase of approximately $6.7 million related to legal and consulting costs associated with the Company's separation from Ironwood, an increase of approximately $4.0 million in compensation, benefits and other employee-related expenses, an increase of approximately $1.0 million related to recruiting costs and other professional service costs, an increase of approximately $0.3 million in costs related to workforce reduction allocated to general and administrative expenses, and an increase of approximately $0.3 million in costs related to facilities and information technology infrastructure.

Liquidity and Capital Resources

Historically, the primary source of liquidity for our business was cash flow allocated to Cyclerion from Ironwood. Prior to separation, transfers of cash to and from Ironwood have been reflected in Net Parent Investment in the historical combined balance sheets, statements of cash flows and statements of changes in Net Parent Investment. We have not reported cash or cash equivalents for the periods presented in the combined balance sheets.

After giving effect to the completion of the separation on April 1, 2019 and the closing of the private placement on April 2, 2019, our cash and cash equivalents are approximately $165.0 million, which is equal to the aggregate cash investment in the private placement, after the payment of certain separation-related expenses. Subsequent to the separation, we no longer participate in Ironwood's centralized cash management or benefit from direct funding from Ironwood. Our ability to fund our operations and capital needs will depend on our ongoing ability to generate cash from operations and access to capital markets and other sources of capital, as further described below. We anticipate that our principal uses of cash in the future will be primarily to fund our operations, working capital needs, capital expenditures and other general corporate purposes.

Going Concern

The financial statements have been prepared assuming that we will continue as a going concern. We have experienced negative cash flows from operations for all historical periods presented and expect these losses to continue into the foreseeable future as we operate as a separate, publicly traded company and continue the development and clinical testing of our lead product candidates, olinciguat, praliciguat and IW-6463, as well as our discovery research programs for serious and orphan liver and lung diseases. These conditions raise substantial doubt about our ability to continue as a going concern. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Subsequent to December 31, 2018, but prior to April 9, 2019, certain events have occurred, and have been documented in Note 11 Subsequent Events of the accompanying financial statements, which have caused us to re-evaluate our ability as a going concern. On April 1, 2019, Ironwood completed the previously announced separation of its soluble guanylate cyclase business, and certain other assets and liabilities, into a separate, independent publicly traded company by way of a pro-rata distribution of all of the outstanding shares of our common stock through a dividend distribution of one share of our common stock, with no par value per share, for every 10 shares of Ironwood common stock held by Ironwood stockholders as of the close of business on March 19, 2019, the record date for the distribution. As a result of the separation, we became an independent public company and commenced regular way trading under the symbol "CYCN" on the Nasdaq Global Select Market on April 2, 2019. On April 2, 2019, the Company issued 11,817,165 shares ("Private Placement Shares") of its common stock to accredited investors for gross proceeds of $175.0 million (net proceeds of $165.00 million) pursuant to the Amended and Restated Common Stock Purchase Agreement, dated February 25, 2019. The funds associated with the sale of Private Placement Shares was received by the Company as of April 2, 2019, and as a result, the substantial doubt surrounding the Company's ability to continue as a going concern (as discussed in Note 1) has been alleviated. As of April 2, 2019, though we expect negative cash flows to continue through 2019 as we continue the development and clinical stage testing of our product candidates and our discovery research programs, we expect to be able to fund operating expenses and capital expenditure requirements through the first quarter of 2021.

Cash Flows from Operating Activities

Net cash used in operating activities totaled approximately $97.5 million for the year ended December 31, 2018. The primary uses of cash were our net loss of $115.3 million and changes in assets

of approximately $0.4 million resulting primarily from an increase in prepaid expenses and other current assets. These uses of cash were primarily offset by non-cash items of approximately $13.9 million, including approximately $12.4 million in share-based compensation expense and approximately $1.5 million in depreciation and amortization expense of property and equipment, and changes in liabilities of approximately $3.4 million resulting primarily from increases in accounts payable, accrued research and development costs, and accrued expenses and other current liabilities of approximately $1.0 million, $0.4 million and $2.0 million, respectively.

Net cash used in operating activities totaled approximately $81.2 million for the year ended December 31, 2017. The primary uses of cash were our net loss of $93.9 million and changes in assets of approximately $1.0 million resulting primarily from an increase in prepaid expenses. These uses of cash were primarily offset by non-cash expenses of approximately $11.2 million, including approximately $9.5 million in share-based compensation expense and approximately $1.7 million in depreciation and amortization expense of property and equipment, and changes in liabilities of approximately $2.5 million resulting primarily from increases in accounts payable and accrued research and development costs of approximately $0.4 million and approximately $2.7 million, respectively, offset by a decrease in accrued expenses and other current liabilities of approximately $0.6 million.

Cash Flows from Investing Activities

Cash used in investing activities for the years ended December 31, 2018 and December 31, 2017 totaled approximately $3.4 million and approximately $1.4 million, respectively, resulting primarily from the purchase of property and equipment, primarily laboratory equipment.

Cash Flows from Financing Activities

As Ironwood managed our cash and financing arrangements prior to the completion of the separation on April 1, 2019, all excess cash generated through earnings prior to April 1, 12019 was deemed remitted to Ironwood and all sources of cash were deemed funded by Ironwood.

Cash provided by financing activities for the year ended December 31, 2018 was approximately $100.9 million, as compared to approximately $82.6 million for the year ended December 31, 2017, primarily as a result of cash transferred to us from Ironwood based on changes in our cash used for operations.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates. In addition, we have and expect to continue to incur additional costs associated with operating as a public company. Our expenses will also increase as we:

- leverage our programs to continue advancing our product candidates into preclinical and clinical development;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- hire additional clinical, quality control and scientific personnel;
- expand our operational, financial and management systems and increase personnel, including personnel to support our clinical development and our operations as a public company; and
- maintain, expand and protect our intellectual property portfolio.

We believe that our initial cash capitalization from the closing of the private placement will enable us to fund our operating expenses and capital expenditure requirements through the first quarter of

2021. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See "Certain Relationships and Related Party Transactions—Private Placement."

Because of the numerous risks and uncertainties associated with research, development and commercialization of product candidates, we are unable to estimate the exact amount of our working capital requirements. Our future funding requirements will depend on, and could increase significantly as a result of, many factors, including:

- the scope, progress, results and costs of researching and developing our product candidates, and conducting preclinical studies and clinical trials;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of future activities, including medical affairs, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- the cost and timing of hiring new employees to support our continued growth;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- the timing, receipt and amount of sales of, or milestone payments related to or royalties on, our current or future product candidates, if any.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. Further, our operating plans may change in the future, and we may need additional funds to meet operational needs and capital requirements associated with such operating plans.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic alliances or licensing arrangements with third parties. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest may be materially diluted, and the terms of such securities could include liquidation or other preferences that adversely affect your rights as a common shareholder. Debt financing and preferred equity financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specified actions, such as incurring additional debt, making capital expenditures or declaring dividends. In addition, debt financing would result in increased fixed payment obligations.

If we raise funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us.

If we are unable to raise additional funds when needed, we may be required to delay, reduce or eliminate our product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Commitments and Obligations

Tax-related Obligations

We exclude assets or liabilities or obligations pertaining to uncertain tax positions from our summary of contractual commitments and obligations as we cannot make a reliable estimate of the period of cash settlement with the respective taxing authorities. As of December 31, 2017 and 2018, we had no uncertain tax positions, as described more fully in Note 7, *Income Taxes*, of the combined financial statements appearing elsewhere in this prospectus.

Other Funding Commitments

As of December 31, 2017 and 2018, we have several ongoing studies in various clinical trial stages. Our most significant clinical trial expenditures are to clinical research organizations, or CROs. The contracts with CROs generally are cancellable, with notice, at our option and do not have any significant cancellation penalties.

Transition from Ironwood and Costs to Operate as an Independent Company

The combined financial statements reflect our operating results and financial position as it was operated by Ironwood, rather than as an independent company. We will incur additional ongoing operating expenses to operate as an independent company. These costs will include the cost of various corporate headquarters functions, incremental information technology-related costs and incremental costs to operate stand-alone accounting, legal and other administrative functions. We will also incur non-recurring expenses and non-recurring capital expenditures.

As an independent company, our information technology operating costs may be higher than the costs allocated in the historical combined financial statements. In addition, we will incur non-recurring expenses and capital expenditures to establish independent information technology systems.

We are currently building our accounting and other administrative infrastructure. We entered into a transition services agreement with Ironwood that will provide us with certain services and resources related to corporate functions for an initial term of between one to two years (as applicable). This transition services agreement will allow us to operate our business independently prior to establishing stand-alone infrastructure. During the transition from Ironwood, we will incur non-recurring expenses to expand its infrastructure.

It is not practicable to estimate the costs that would have been incurred in each of the periods presented in the historical financial statements for the functions described above. Actual costs that would have been incurred if we operated as a stand-alone company during these periods would have depended on various factors, including organizational design, outsourcing and other strategic decisions related to corporate functions, information technology and back office infrastructure.

Transactions with Related and Certain Other Parties

Prior to or concurrently with the completion of the separation, we entered into certain agreements with Ironwood resulting from and relating to the separation, including a separation agreement, two transition services agreements, a development agreement, a tax matters agreement, an intellectual property license agreement and an employee matters agreement. The terms of these agreements, including information on the business purpose of such agreements, transaction prices, related ongoing contractual commitments and any related special risks or contingencies are discussed in greater detail under "Certain Relationships and Related Party Transactions" appearing elsewhere in this prospectus.

Off-Balance Sheet Arrangements

We do not have any relationships with unconsolidated entities or financial partnerships, such as entities often referred to as structured finance or special purpose entities, that would have been established for the purpose of facilitating off-balance sheet arrangements (as that term is defined in Item 303(a)(4)(ii) of Regulation S-K) or other contractually narrow or limited purposes. As such, we are not exposed to any financing, liquidity, market or credit risk that could arise if we had engaged in those types of relationships. We enter into guarantees in the ordinary course of business related to the guarantee of our own performance.

New Accounting Pronouncements

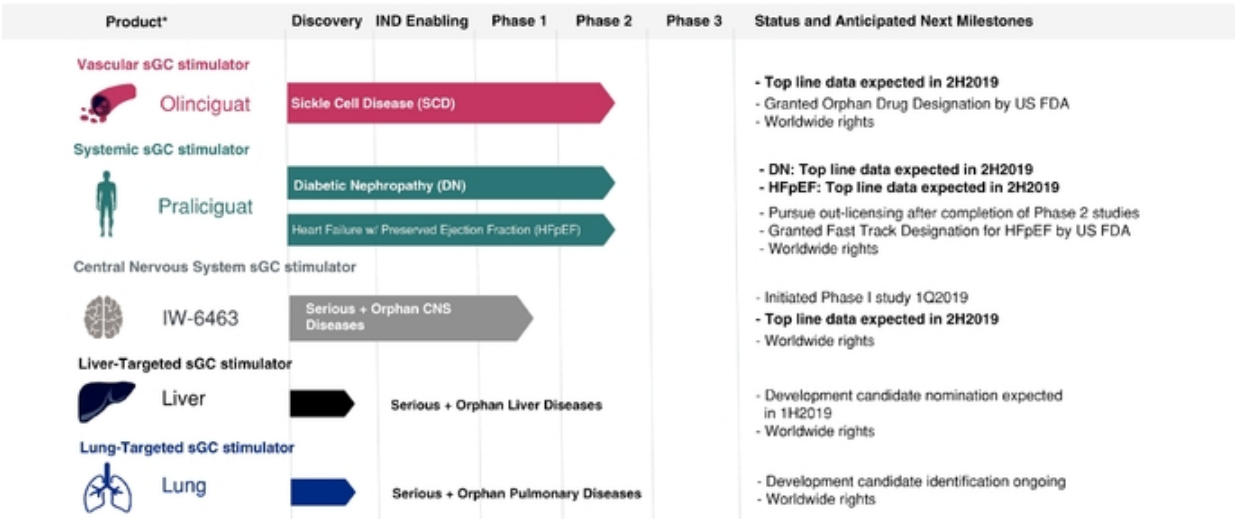
For a discussion of new accounting pronouncements see Note 2, *Summary of Significant Accounting Policies*, of the combined financial statements appearing elsewhere in this prospectus.

BUSINESS

Overview

We are a clinical-stage biopharmaceutical company harnessing the power of soluble guanylate cyclase, or sGC, pharmacology to discover, develop and commercialize breakthrough treatments for serious and orphan diseases. Our focus is enabling the full therapeutic potential of next-generation sGC stimulators. sGC stimulators are small molecules that act synergistically with nitric oxide on sGC to boost production of cyclic guanosine monophosphate, or cGMP. cGMP is a key second messenger that, when produced by sGC, regulates diverse and critical biological functions throughout the body including blood flow and vascular dynamics, inflammatory and fibrotic processes, metabolism and neuronal function. We believe that the key to unlocking the full therapeutic potential of the nitric oxide-cGMP pathway is to design differentiated next-generation sGC stimulators that preferentially modulate pathway signaling in tissues of greatest relevance to the diseases they are developed to treat. This targeted approach is intended to maximize the potential benefits of nitric oxide-cGMP pathway stimulation in disease-relevant tissues. We are led by an accomplished team, many of whom have worked together previously at Pharmaceuticals, Inc., or Ironwood, with an exceptional track record of discovering, developing and commercializing meaningful therapies for patients while creating value for stockholders. Our strategy rests on a solid scientific foundation that is enabled by our people and capabilities, external collaborations and a responsive capital allocation approach.

We have an extensive portfolio of five differentiated sGC stimulator programs with several pipeline catalysts expected in 2019. The following table summarizes our programs:



Status of selected key development programs as of April 8, 2019. Represents current phase of development, does not correspond to the completion of a particular phase.

Strategic Core

We leverage the therapeutic potential of nitric oxide signaling by modulating the nitric oxide-cGMP pathway via pharmacologically tailored sGC stimulation. Nitric oxide signaling plays a central role in regulating diverse aspects of human physiology throughout the body, including vascular smooth muscle tone and blood flow, as well as processes that influence inflammation, fibrosis, metabolism and neuronal function. Deficient nitric oxide signaling is linked to a wide range of cardiovascular, metabolic, inflammatory, fibrotic and neurological diseases. Stimulation of sGC is clinically validated by ADEMPAS®, an sGC stimulator marketed by Bayer, that represents an important first step in demonstrating the therapeutic potential of this mechanism. In order to realize the significant potential of sGC stimulation to enable the development of important new medicines, we are focused on developing next generation sGC stimulators.

We design sGC stimulators with distinct pharmacologic and biodistribution properties that preferentially enhance nitric oxide-cGMP signaling in target tissues of greatest relevance to the diseases they are developed to treat. The resulting sGC stimulators are highly differentiated from each other, as well as from other sGC modulators and molecules that target this pathway via other mechanisms. This approach to the therapeutic application of nitric oxide-cGMP pharmacology is intended to allow us to harness the powerful multidimensional pharmacology of sGC stimulation for clinical application in serious and orphan diseases.

We have discovered and are advancing a pipeline of five differentiated sGC stimulator programs whose properties are tailored for distinct serious and orphan diseases with significant unmet clinical need.

- ***Olinciguat is an orally administered, once-daily, vascular sGC stimulator*** that we believe is well suited for the treatment of sickle cell disease, or SCD, given its distribution to the vasculature and highly perfused organs, such as the kidney and lungs, which are frequently affected by this

disease. SCD is a genetic disease that causes red blood cells to "sickle," or become misshapen, and to more easily rupture, ultimately resulting in severe complications including chronic vascular inflammation, painful vaso-occlusive crises, or VOCs, poor blood flow to organs, pulmonary hypertension and renal failure. Patients with SCD have a shortened life expectancy, with an average of 42 years for males and 48 years for females in the United States. SCD affects approximately 100,000 people in the United States and approximately 50,000 in the EU5, or France, Germany, Italy, Spain and the United Kingdom. The global incidence of SCD is estimated to affect approximately 300,000 children born annually. By amplifying nitric oxide signaling, we believe that olinciguat has the potential to reduce the proportion of sickled cells, decrease vascular inflammation and cell adhesion, and improve nitric oxide-mediated vasodilation. For patients with SCD, we believe this may translate into reduction in debilitating daily symptoms such as chronic pain and fatigue, decrease in anemia, reduction in painful VOCs and end-organ protection (especially for the kidney, heart and lung) potentially leading to an increase in survival. Olinciguat has been granted Orphan Drug Designation for SCD by the U. S. Food and Drug Administration, or FDA, and is currently in a Phase 2 study, STRONG-SCD, that is expected to enroll approximately 88 patients. Following the completion of our ongoing Phase 2 study, should data warrant, we intend to advance olinciguat into late-stage development for SCD and, if approved, commercialize on our own in the United States and alone or through licensing arrangements with partners around the world. We expect results from this study in the second half of 2019.

- ***Praliciguat is an orally administered, once-daily systemic sGC stimulator*** that we believe is well suited for the treatment of serious cardiometabolic diseases given its very extensive distribution into tissues, particularly adipose, kidney, heart and liver. We believe this distribution profile is essential to realize the potential of sGC pathway pharmacology to treat cardiometabolic diseases that are characterized by adipose inflammation, metabolic dysfunction and associated multi-organ etiology and involvement. We are assessing the potential of praliciguat to treat two such diseases: diabetic neuropathy, or DN, and heart failure with preserved ejection fraction, or HFpEF.

  There are over 400 million adults with diabetes globally at a prevalence rate of 8.5%. Up to 40% of all patients with diabetes have DN. In patients with diabetes, nephropathy is a major risk factor for cardiovascular disease, the major driver of excess cardiovascular mortality, and the single strongest predictor of mortality. DN is progressive, and patients that survive to end-stage renal disease, or ESRD, require chronic dialysis treatment or kidney transplant. We believe praliciguat may help treat DN by enhancing renal endothelial function and blood flow regulation and attenuating renal inflammation and fibrosis. Praliciguat is currently in a dose-ranging Phase 2 study that is expected to enroll approximately 150 adult patients with DN. We expect results from this study in the second half of 2019.

  Heart failure remains a rising global epidemic with an estimated prevalence of approximately 38 million individuals globally. HFpEF comprises 44% to 72% of new heart failure diagnoses and accounts for approximately half of the heart failure hospitalizations, with frequent readmissions. Five-year mortality rates for patients with HFpEF have been reported to range from 55% to 74%. We believe praliciguat, by enhancing impaired nitric oxide signaling in the heart and systemic circulation, has the potential to improve coronary blood flow, increase oxygen delivery to and utilization by skeletal muscle, and over the longer term, reduce cardiac stiffness and microvascular inflammation to both improve symptoms and potentially slow or halt disease progression. Praliciguat was granted Fast Track Designation for the treatment of HFpEF by the FDA and is in a Phase 2 proof-of-concept trial, CAPACITY-HFpEF, that is expected to enroll approximately 184 patients. We expect results from this study in the second half of 2019.

Following completion of ongoing Phase 2 studies, should data warrant, we intend to pursue out-licensing of praliciguat for late-stage development and commercialization in DN, HFpEF and potentially additional cardiovascular/metabolic indications.

- ***IW-6463 is an orally administered CNS-penetrant sGC stimulator*** that, because it readily crosses the blood-brain barrier, affords an unprecedented opportunity to expand the utility of sGC pharmacology to serious neurodegenerative diseases. Clinical and nonclinical research suggests that nitric oxide signaling plays a critical role in the central nervous system, or CNS, in memory formation and retention, control of cerebral blood flow and modulation of neuroinflammation. Nitric oxide is a potent neurotransmitter, and impaired nitric oxide-sGC-cGMP signaling is believed to play an important role in the pathogenesis of several neurodegenerative diseases. In preclinical models, IW-6463 has been associated with an increase in cerebral blood flow, improved neuronal health and function, reduced markers of neuroinflammation and enhanced cognition. CNS pharmacological activity of IW-6463 has been observed preclinically using multiple non-invasive techniques that can also be employed in early human clinical studies. Our first-in-human study of IW-6463 initiated in January of 2019 with results expected in the second half of 2019.

- ***Our liver-targeted sGC stimulator*** will be orally administered and designed to selectively partition to the liver. By achieving liver concentrations many fold higher than corresponding plasma concentrations, we intend to maximize hepatic pharmacology. In animal models of liver fibrosis treated with systemic sGC stimulators, we have observed reductions in liver fibrosis, inflammation and steatosis, pathophysiological processes that underlie multiple chronic liver diseases. We expect to nominate a development candidate in the second quarter of 2019 and progress to filing an Investigational New Drug/Clinical Trial Application, or IND/CTA, thereafter.

- ***Our lung-targeted sGC stimulator*** will be administered via inhalation and will be aimed at realizing the full potential of sGC stimulation in pulmonary diseases by selectively increasing exposure in the lung. Preclinically, our lead molecule is highly retained in the lung with greater than 50-fold selectivity for lung over plasma. In addition, in preclinical studies, the lead molecule is metabolically stable in the lung, whereas it is unstable in the plasma with rapid systemic clearance. We are pursuing the identification of a development candidate, and expect to progress to filing an IND/CTA, thereafter.

We have a comprehensive intellectual property strategy to protect our platform and related proprietary technology that covers composition of matter, method of use, formulations and process development. The molecules and technologies underlying our sGC patents and pending patent applications were discovered and developed by our internal team of scientific experts.

Value-Creating Enablers

People and capabilities

We are leaders in targeted sGC stimulator chemistry and nitric oxide-cGMP pathway pharmacology. Our founding team has deep knowledge and significant experience in cGMP pathway research and development, from the discovery and development of LINZESS®, an Ironwood product that leverages the pharmacology of the guanylate cyclase-C-cGMP pathway, to the development of the sGC stimulator chemistry libraries and systems pharmacology data that gave rise to the current portfolio of assets and will serve as the foundation for our future innovation. This knowledge and experience, centered on a single scientific mechanism with rich pharmacology, underpins our unique ability to identify opportunities and design sGC stimulators tailored for specific serious diseases.

We have an exceptional team with a proven track record at all levels within our organization. We have broad expertise throughout our organization in discovering, developing and commercializing category-leading products, and are led by a management team with a history of success delivering innovative therapies to patients while creating value for stockholders. Our research and development leadership has been involved in the development and submission of over 100 IND/CTA applications and 20 New Drug Applications, NDA/Marketing Authorization Applications for approval of products

based on novel chemical entities. They have more than 200 years of combined experience at pharmaceutical and biotechnology companies and have all worked together previously at Ironwood.

- **Our Chief Executive Officer, Peter Hecht, Ph.D.,** served as Ironwood's Chief Executive Officer and a director since co-founding the company in 1998. During that time, he built a highly respected leadership team and culture that worked together to discover, develop and commercialize LINZESS®, a novel first-in-mechanism therapeutic that quickly became the branded prescription market leader in its class and has been taken by millions of patients for irritable bowel syndrome with constipation and chronic idiopathic constipation. Additionally, during his tenure the team pioneered new areas of science, produced a development portfolio with multiple innovative drug candidates, and established a valuable network of global partnerships. Through a combination of private and public equity, structured debt, and partnerships, Dr. Hecht and his team raised over one billion dollars to fund these efforts.

- **Our President, Mark Currie, Ph.D.**, has made critical scientific contributions over the last 40 years that have greatly advanced understanding of the pharmacology of nitric oxide, guanylate cyclases and cGMP signaling. Dr. Currie has led the characterization and discovery of three hormones that regulate cGMP, atrial natriuretic peptide, guanylin and uroguanylin. These discoveries played a role in the creation of novel treatments for a broad range of diseases including congestive heart failure, acute and chronic pain conditions associated with arthritis, and, more recently, a novel approach to treat patients with painful gastrointestinal conditions. Dr. Currie is the primary inventor of LINZESS®. Prior to joining our team, Dr. Currie led R&D at Ironwood where, in addition to developing LINZESS®, his team created the sGC platform that enabled the creation of Cyclerion. Prior to Ironwood, Dr. Currie led the discovery group at Sepracor Inc., or Sepracor, and discovery pharmacology at Monsanto/Searle, which produced several important medicines, including LUNESTA® and CELEBREX®.

- **Our Head of Global Development, Christopher Wright, M.D., Ph.D.,** has two decades of medical research and drug development experience in orphan and specialty diseases, including cystic fibrosis, hepatitis C, rheumatoid arthritis, epilepsy and dementia. While at Vertex, Dr. Wright oversaw the development of ORKAMBI® through Phase 3, and the successful development and rapid approval of KALYDECO®, a life-changing cystic fibrosis therapy, by the FDA, EMA and other health authorities. He also played an important role in the global development and approval of INCIVEK® for hepatitis C. Prior to joining our team, Dr. Wright led the global development organization at Ironwood, including responsibility for advancing the late-stage and life-cycle gastrointestinal programs as well as the five sGC stimulator programs that underlie Cyclerion's strategic core. Dr. Wright is also a practicing neurologist at Brigham and Women's Hospital in Boston, MA.

- **Our Chief Financial Officer, William Huyett**, has extensive experience in pharmaceutical and medical device corporate strategy, capital allocation, finance, product development and commercialization and corporate leadership gained during his 30-year career at McKinsey and Company, Inc. He joins us from Ironwood, where he served as Chief Operating Officer, and led the efforts to separate our portfolio of sGC stimulator programs into Cyclerion.

External collaboration

We leverage a diverse cross-disciplinary network of external advisors and experts to advance our drug candidates. We do this in three ways. First, we actively engage leading experts to access additional technologies and expertise to advance our programs. This includes collaborations on preclinical models as well as accessing key technologies that can be used in preclinical or clinical studies. We are seasoned collaborators with a history of practical and productive short-term partnerships as well as profitable long-term alliances. Second, we establish disease-area advisory boards of physicians, patients and payors

to provide insights into the unmet medical need and to support the design of clinical trials. Finally, we use a pharmaceutical advisory board made up of veteran drug hunters with broad industry experience and a track record of innovation to help us refine our R&D strategy.

We will apply a "best-owner" approach to our compounds whereby we develop and commercialize product candidates independently or through a partner depending on which path we believe will offer the greatest risk-adjusted value for our stockholders and accelerate global patient access to our drugs. We intend to prioritize development and commercialization in diseases characterized by structurally attractive markets where we can successfully commercialize on our own. We define structurally attractive markets as those managed by a narrow prescriber base with clear unmet patient need, payor willingness to pay and the potential for first-in-class entry. Olinciguat in SCD meets our definition of a structurally attractive market and therefore, we plan to retain the rights to develop and commercialize on our own in the United States and in select global markets. In contrast, due to the broad prescriber base associated with cardiometabolic indications, we intend to pursue out-licensing of the global rights of praliciguat after completion of our ongoing Phase 2 trials to a company with therapeutic-area leadership who can effectively and efficiently execute late-stage development and commercialization. At this time, we do not have any partnerships for any of our product candidates and we intend to apply this "best owner approach" as we make decisions regarding potential partnerships.

Capital allocation and economics

The capital allocation decision making and financial management we use in our business will enable us to continually deploy capital and people to the most promising opportunities. Highlights of our capital allocation and financial management strategy include:

- **Decisive capital allocation:** We plan to establish a high threshold for therapeutic differentiation and compelling business case in each program. We expect to fund clinical trials that are designed to enable decisions to advance or halt the program.

- **Elastic, externalized cost structure:** Our experienced team will seek to use outside supplier/partners wherever possible, in order to benefit from any economies-of-scale and skill sets that such suppliers and partners provide while minimizing our fixed costs.

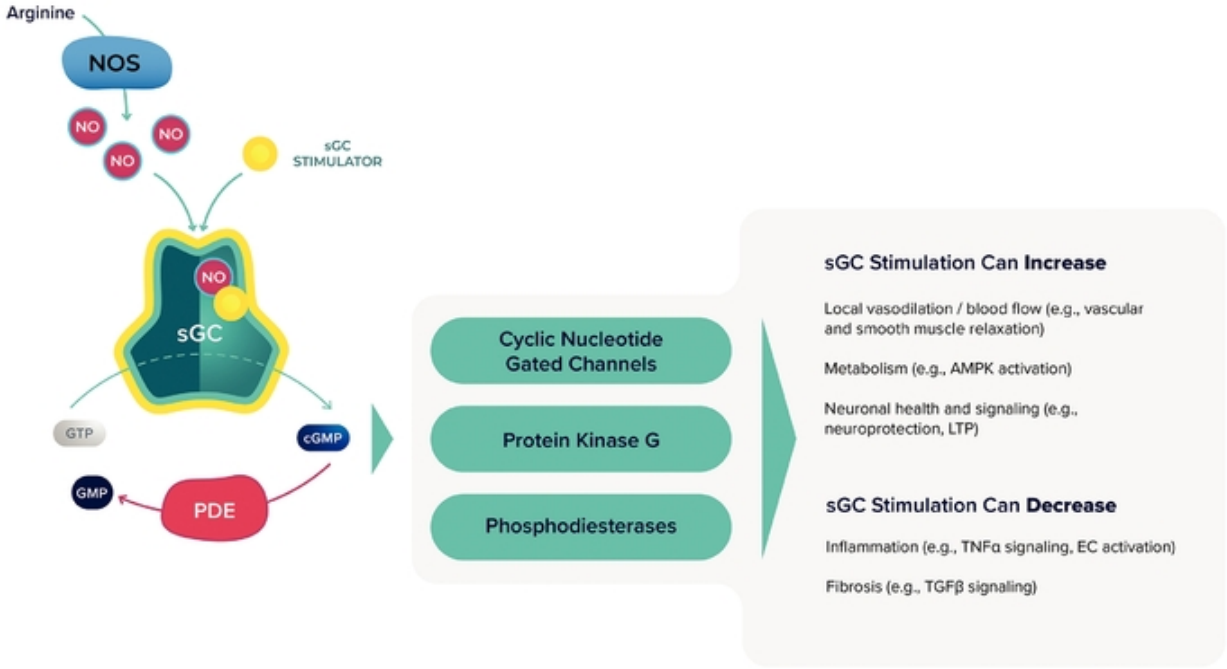
- **Mission-appropriate infrastructure:** Our infrastructure is designed to meet the needs of a multi-program development company intent on prosecuting and developing the sGC mechanism, generating and protecting key intellectual property, compliance and attracting and retaining talent to further advance our five lead sGC stimulator programs and discover additional disease-targeted sGC stimulators.

- **Development program-based management structure:** Our program leaders are accountable for performance against goals for each program based on clinical and scientific, cost and timeline performance metrics.

Our Opportunity—sGC Stimulation

Nitric oxide is a short-lived signaling molecule that is produced locally under exquisite physiological control throughout the body. Nitric oxide signaling plays a central biological role in real-time regulation of diverse systems, the discovery of which was recognized as the basis for the 1998 Nobel Prize in Physiology or Medicine. Nitric oxide signaling is mediated through its receptor, sGC, an intracellular protein in tissues throughout the body, including in the vasculature, kidney, brain, lung, intestines, heart, liver, adipose, spleen and skeletal muscle. As locally produced nitric oxide diffuses into adjacent target cells, it binds to sGC, increasing production of the secondary signaling molecule cGMP. cGMP acts through multiple downstream targets to elicit functional effects. The figure below aggregates the most well-characterized effects of nitric oxide-sGC-cGMP signaling across multiple cell

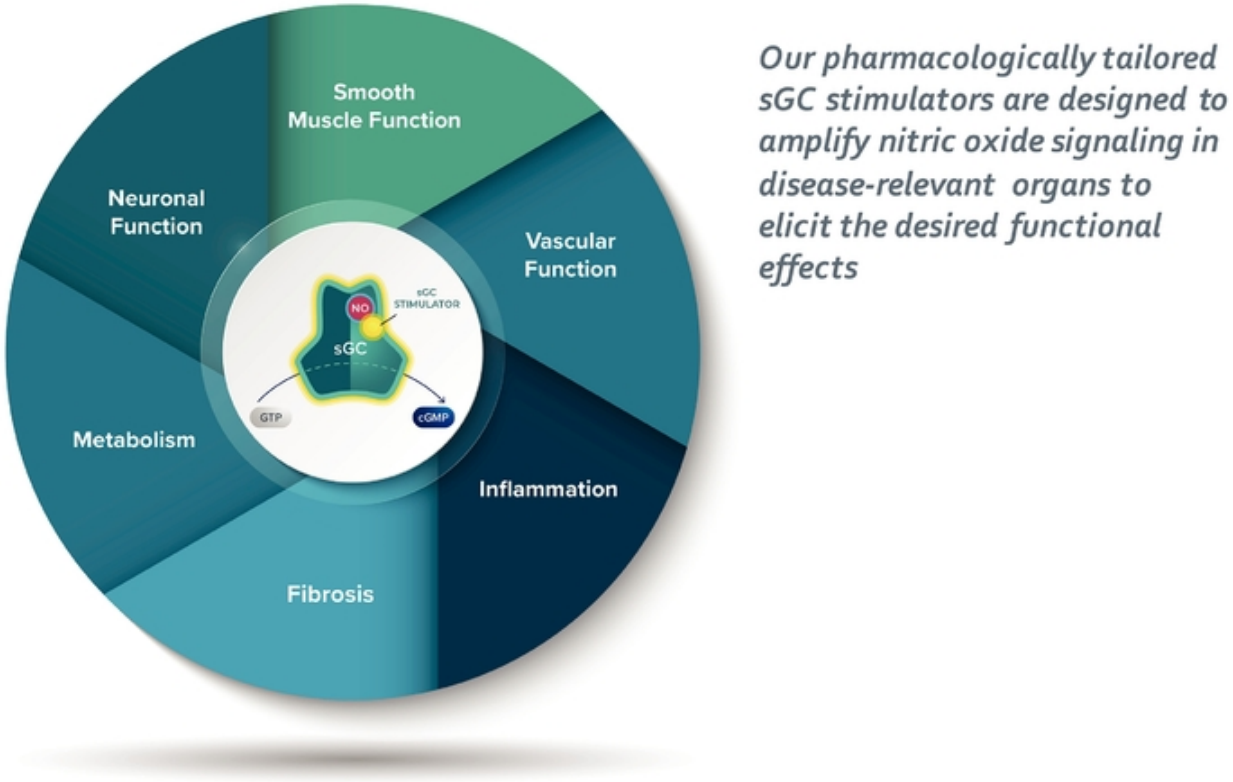
types and tissues. The specificity of nitric oxide signaling in health (*i.e.*, not all of the pathways are activated in all tissues at all times) is accomplished by both local production of nitric oxide and control of the expression and activity of pathway components in distinct cell types. Our approach to capitalize on the breadth of this pathway's potential is to design small molecule sGC stimulators that, by their unique properties, preferentially increase nitric oxide signaling in the tissues most relevant to the diseases they are intended to treat to elicit some or all of the functional effects listed in the figure below.



AMPK=adenosine monophosphate-activated protein kinase;
cGMP=cyclic guanosine monophosphate;
CNGs=cyclic nucleotide-gated channels;
GC=guanylate cyclase;
GTP=guanosine triphosphate;
EC=endothelial cell;
LTP=long-term potentiation;
NO=nitric oxide;
NOS=nitric oxide synthase;
PDE=phosphodiesterase;
PKG=protein kinase G;
sGC=soluble guanylate cyclase;
TGF=transforming growth factor;
TNF=tumor necrosis factor

The effects of nitric oxide signaling on vascular smooth muscle tone and blood flow are well characterized and long known. The therapeutic utility of this pathway was first established in the late 1800s with the use of the nitric oxide-generating compound, nitroglycerin, to relieve angina. More recently, agents that act at different steps of this pathway to increase cGMP levels have been developed as therapies for erectile dysfunction *(e.g.*, the phosphodiesterase type 5, or PDE5, inhibitors, VIAGRA® and CIALIS®) and for two types of pulmonary hypertension, Pulmonary Arterial Hypertension, or PAH, and Chronic Thromboembolic Pulmonary Hypertension, or CTEPH (*e.g.*, the PDE5 inhibitors REVATIO® and ADCIRCA® and the sGC stimulator ADEMPAS®).

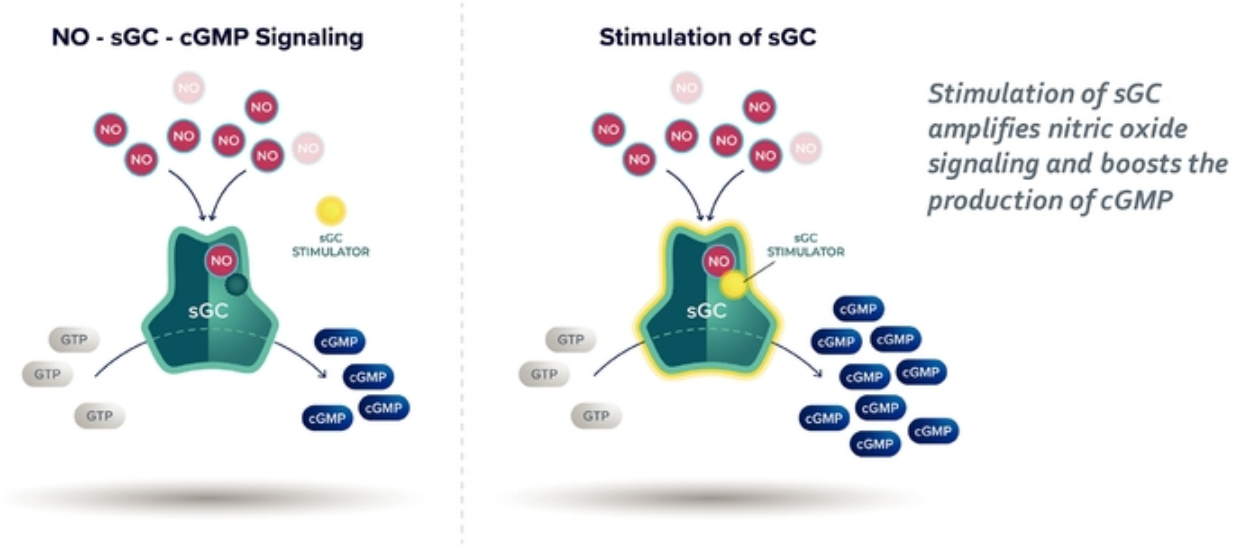
In addition to controlling blood flow, nitric oxide signaling independently regulates processes that influence fibrosis, inflammation and neuronal function. Our team recently extended known nitric oxide signaling pharmacology with the demonstration of clinical effects on metabolism, including fasting plasma glucose, cholesterol and triglycerides, in type 2 diabetic patients with hypertension (refer to figure "*In a Phase 2a study, patients with type 2 diabetes and hypertension on standard of care treatment regimen who received praliciguat for two weeks had improvements in multiple metabolic parameters*").



A wide range of cardiovascular, metabolic, inflammatory, fibrotic and neurological diseases are associated with deficient nitric oxide signaling. When the bioavailability of endogenous nitric oxide is reduced in disease states, normal physiological function is disrupted and signaling pathways are imbalanced, leading to vasoconstriction, inflammation and fibrosis. We believe restoring this signaling pathway represents a potential therapeutic target for powerful pharmacological intervention in many serious diseases. In addition, as described further below, we believe that our approach to enhancing signaling through the nitric oxide-cGMP pathway will also be relevant in diseases in which signaling may not be compromised but for which the resultant pharmacology of enhanced signaling could bring therapeutic benefit.

We believe that the growing understanding of the nitric oxide-cGMP signaling pathway's role in diverse aspects of health and disease creates the potential for a new generation of important therapeutics for serious and orphan diseases that we believe remains largely untapped. Further, we believe that, of the clinically validated means to modulate nitric oxide-cGMP pathway signaling (nitric oxide-generating compounds, PDE5 inhibitors and sGC stimulators), sGC stimulation represents the optimal mechanism by which to realize the full therapeutic potential of this pathway. Direct nitric oxide-generating compounds, such as nitroglycerin and nitrates, have limitations including tolerance (attenuation of effect over time), which has not been observed for sGC stimulators. PDE5 inhibitors rely on basal signaling (flux) through the pathway to have effects, which limits the pharmacological

effect they can have. In contrast, sGC stimulators are agonists of sGC that work synergistically with nitric oxide to amplify signaling through the pathway, providing opportunity to expand the pharmacology to any tissue in which nitric oxide signaling is occurring.



Adapted from Tobin, Zimmer et al.2018. J. Pharmacol. Exp. Therapeut., 365 (3). 664-675

Stimulation of sGC is clinically validated by ADEMPAS®, an oral, three times-daily administered sGC stimulator marketed by Bayer, that is approved for the treatment of PAH and CTEPH, both progressive life-threatening diseases that are linked to deficiencies in the nitric oxide signaling pathway. ADEMPAS® represents an important first step in demonstrating the therapeutic potential of this mechanism.

In order to realize the significant potential of sGC stimulation to enable the development of important new medicines, we are focused on developing next generation sGC stimulators. Our sGC stimulators act as *directed* agonists, meaning they are designed to boost signaling within the context of the endogenous nitric oxide pathway in a localized, tailored manner.

Importantly, the potential utility of sGC stimulation is not restricted to diseases associated with a loss of nitric oxide signaling. Because sGC stimulators act as agonists, like b-agonists and steroids, they do not require an underlying defect in the pathway to have a pharmacological effect. They are able to enhance the activity of a fully functional nitric oxide signaling pathway to generate pharmacological effects. Preclinical studies suggest that enhanced nitric oxide pathway signaling may provide therapeutic benefit in diseases associated with inflammation, fibrosis or metabolic dysregulation, regardless of whether there is a direct role for the nitric oxide pathway dysfunction in the pathogenesis of the disease.

We believe the breadth of potential applications for sGC stimulators is generally analogous to many aspects of the history of corticosteroids. While sGC stimulators have not been studied as extensively as corticosteroids, we believe the development history for this broad class of agonist drugs is instructive regarding the potential for sGC stimulators, which also act as agonists, to one day have broad application across diseases targeting multiple different tissues and systems. The targets for both sGC stimulators and corticosteroids are found in tissues throughout the body where they regulate fundamental signaling pathways with wide-ranging downstream effects. In this context, first-generation broadly distributed compounds with powerful pharmacology are suited for systemic disorders whereas organ-targeted compounds can enable greater activation in target tissues while minimizing systemic effects. This affords the opportunity to develop not only multiple systemic products but also a wide

range of specific tissue-targeted products. In the 1950s, first-generation systemic corticosteroids were developed following the discovery of the hormone cortisol. Powerful systemic corticosteroids such as prednisone are still used extensively today in the treatment of serious systemic conditions, including lupus, lymphomas and Crohn's disease; however, the expansion of systemic corticosteroids as a class was limited by effects associated with untargeted delivery. The opportunities associated with developing a mechanism for selective delivery of an agonist are illustrated by the proliferation of whole new categories of second-generation corticosteroids that target specific organs. For example, topical cortisone for dermal inflammation, inhaled corticosteroids, such as FLONASE®, for asthma and allergies, and rectally administered budesonide, such as UCERIS® for ulcerative colitis, have all had commercial success.

As was done to harness the powerful pharmacology of corticosteroids, we believe the key to unlocking the full potential of sGC pharmacology is to develop stimulators that can selectively target this pathway in the tissues of greatest relevance to, and with the optimal pharmacokinetic and pharmacodynamic profile for, the diseases of interest. Olinciguat, our vascular sGC stimulator, is distributed to both the vasculature and key organs such as kidney and lungs, which we believe makes olinciguat well suited for the potential treatment of SCD. Praliciguat, our systemic sGC stimulator, is distinct in its very extensive tissue distribution, including to adipose, which we believe may be particularly relevant to the treatment of cardiometabolic diseases such as DN and HFpEF. In addition, we believe we are the first to discover and develop tissue-targeted sGC stimulators, including IW-6463, a compound that can access the brain for potential to address serious neurodegenerative diseases as well as compounds that can preferentially target the liver or the lung for potential treatment of serious and orphan diseases that primarily affect these organs.

Our Product Candidates

Olinciguat for Sickle Cell Disease

Olinciguat is an orally administered, once-daily, vascular sGC stimulator designed for the treatment of SCD. Because SCD is a hemoglobinopathy with blood vessel and multi-organ involvement, we believe olinciguat's distribution to both the vasculature as well as to highly perfused organs such as the kidney and lungs, makes it particularly well suited for the potential treatment of SCD. We believe olinciguat's long plasma half-life, which results in low fluctuations from one daily dose to the next (*i.e.*, low peak-to-trough ratio), will allow for steady, efficacious concentrations to be maintained below levels that might produce side effects. We have observed very low renal clearance of olinciguat in humans, which we believe is a beneficial attribute for this patient population, as patients with SCD often have compromised renal function. Olinciguat treatment was associated with a decrease in the progression of hemolytic anemia in a mouse model of SCD, higher mRNA expression of the g-globin subunit of fetal hemoglobin in cultured cells and lower levels of vascular inflammatory markers and improved vascular function in mouse models of inflammation. Following the completion of our Phase 1 studies with olinciguat that demonstrated a well-tolerated dose range, dose-proportional pharmacokinetics and target engagement, we initiated a Phase 2 clinical study in patients with SCD. Olinciguat is designed to reduce the proportion of sickled cells, decrease vascular inflammation and cell adhesion, and improve nitric oxide-mediated vasodilation. For patients with SCD, we believe this may translate into a reduction in debilitating daily symptoms such as chronic pain and fatigue, decrease in anemia, reduction in painful events called VOCs, and end-organ protection (especially for kidney, heart and lung), potentially leading to an increase in survival. Olinciguat was granted Orphan Drug Designation for SCD by the FDA in June 2018.

Sickle Cell Disease

Disease Background

SCD encompasses a group of genetic blood disorders affecting hemoglobin, a protein in red blood cells that carries oxygen from the lungs to the body's tissues and returns carbon dioxide from the tissues back to the lungs. SCD varies substantially in presentation and clinical course. An inherited mutation results in substitution of the amino acid valine for glutamic acid in the sixth position of the beta globin chain causing formation of HbS, an atypical form of hemoglobin that can cause red blood cells to change shape, or sickle. There are several genotypes of SCD found globally with the following being most prevalent:

- HbSS: Patients inherit two sickle cell genes ("S"); one from each parent. This is often referred to as "sickle cell anemia" and is usually the most severe form of SCD;
- HbSC: Patients inherit a sickle cell gene ("S") from one parent and an abnormal hemoglobin gene called "C" from the other parent. This is usually a milder form of the disease; and
- HbS/Beta thalassemia: Patients inherit a sickle cell gene from one parent, and a gene for b thalassemia, another form of anemia, from the other parent. There are two types of beta thalassemia: "0" and "+". bthal^{0} is often a more severe form while bthal^{+} is a milder form.

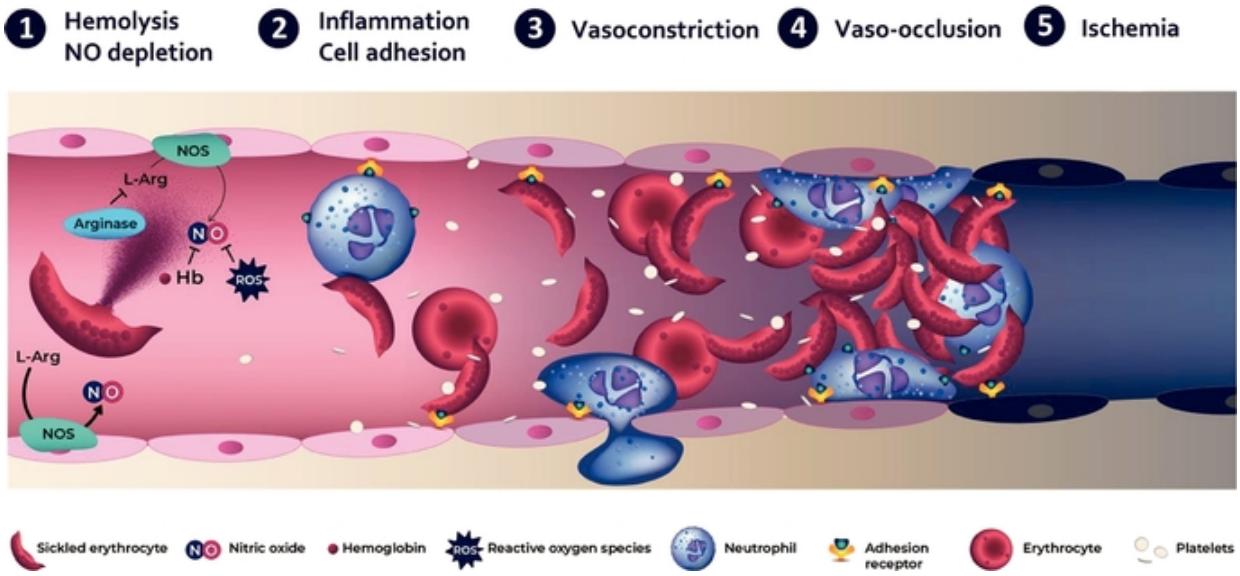
SCD causes lifelong symptoms and complications that generally begin within eight to ten weeks of birth. Painful VOCs are the most reported and recognized complication. Additionally, SCD patients experience many daily symptoms, including chronic pain, fatigue and shortness of breath. Although VOC is the most reported and recognized symptom, SCD affects the entire body. Recurrent episodes of vaso-occlusion and inflammation result in progressive damage to organs, including the brain, kidneys, lungs, bones and cardiovascular system. For example, accumulating damage from both silent cerebral infarcts and overt strokes leads to cognitive impairment, increased pulmonary fibrosis and pulmonary hypertension stress cardiac function and progressive glomerular fibrosis and associated decrease in glomerular filtration rate often lead to renal failure. In fact, nearly one-third of people with SCD will develop chronic kidney disease and some of these patients will develop ESRD. The one-year death rate following an ESRD diagnosis was almost three times higher in people with ESRD due to SCD when compared with those with ESRD from other causes. These cumulative effects lead to a shortened life expectancy with an average of 42 years for males and 48 years for females in the United States.

Current SCD treatment primarily focuses on the management of acute and chronic complications with therapies including antibiotics, anti-inflammatory drugs and blood transfusions. Although chronic transfusions correct anemia and can temporarily resolve painful complication, transfusion carries the risk of iron overload, and therefore, iron chelation therapy becomes a part of a patient's treatment plan in an effort to avoid liver damage. Treatment options that address chronic symptoms and/or underlying pathophysiology are limited. Hematopoietic stem cell transplantation, or HSCT, is the only curative treatment; however, only 10-20% of SCD patients qualify for transplantation. Because of the associated morbidity and mortality and the difficulty in finding a matched donor, HSCT is generally limited to the most severe patients or children with matched siblings. HSCT also does not improve the underlying organ damage that has occurred prior to transplant. Until recently, only one drug, hydroxyurea, was approved by the FDA to reduce the frequency of painful crises and to reduce the need for blood transfusions. Despite recommendations for use in all patients with SCD, few patients are able to continue treatment with hydroxyurea uninterrupted, largely due to its side effects and potential for long-term toxicity. According to the hydroxyurea label, its adverse event profile includes neutropenia and suppression of reticulocytes and platelets, necessitating a temporary cessation in treatment in almost all patients. In 2017, ENDARI™, a pharmaceutical grade oral powder version of the amino acid glutamine, was approved to reduce the acute complications of SCD. According to the ENDARI label, patients treated with placebo for 48 weeks had a median of four pain crises compared with three for

the patients treated with ENDARI. Additionally, many patients are on pain management programs that include chronic opioid therapy; paradoxically however, patients on chronic opioids often experience greater levels of clinical pain as well as depression, fatigue and proportion of days in crisis. In addition, chronic opioid therapy is associated with greater healthcare utilization on both crisis and non-crisis days.

Nitric Oxide Connection

The combined effects of vasoconstriction, inflammation and cellular aggregation and adhesion to the endothelium, the cells that line the interior surface of the vasculature, are believed to contribute to many complications and symptoms of SCD, including VOCs and chronic pain. Over time, these combined effects result in accumulated vascular and tissue damage that can lead to organ failure and shortened life expectancy. Nitric oxide deficiency plays an important role in the pathophysiology that underlies the accumulated damage. HbS, when deoxygenated, polymerizes into rigid chains that deform red blood cells into the characteristic sickle shape. In addition to causing reduced blood flow to organs and tissue, sickled red blood cells are more susceptible to hemolysis, and have an average lifespan of approximately 20 days compared with 120 days for normal red blood cells. As depicted in the figure below, upon hemolysis, hemoglobin and the arginine-metabolizing enzyme arginase are released into the plasma. Cell-free hemoglobin binds with high affinity to nitric oxide in the plasma thereby reducing nitric oxide bioavailability. In addition, arginase degrades arginine, the key substrate for nitric oxide synthesis, which then limits the generation of nitric oxide. Low nitric oxide bioavailability results in reduced cGMP production, which is in turn associated with the vascular inflammation, cell adhesion, vasoconstriction, vaso-occlusion, and ischemia that are responsible for the symptoms and complications of SCD.

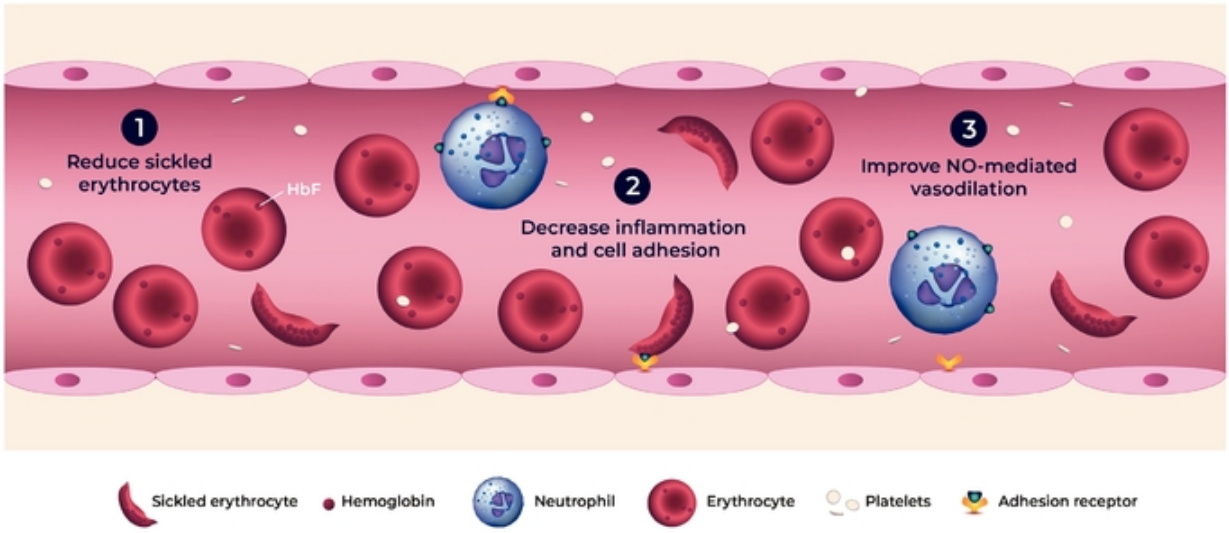


Our Solution

Once-daily olinciguat is designed to address the nitric oxide deficiency that underlies the pathophysiology in SCD by amplifying nitric oxide signaling, which we believe will increase production of HbF, which can inhibit polymerization of HbS and thereby reduce the proportion of sickled red blood cells, decrease vascular inflammation and cell adhesion, and improve nitric oxide-mediated vasodilation, as depicted in the figure below. By these mechanisms, we believe olinciguat may improve the daily symptoms of SCD, including chronic pain and fatigue, as well as decrease anemia, reduce the

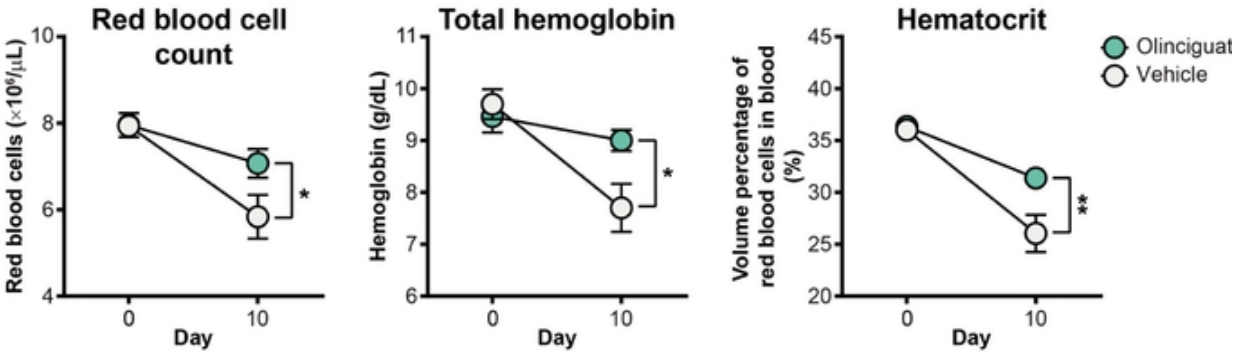
frequency of painful crises and ultimately prolong life by preserving organ function. sGC stimulation by olinciguat expands on the focus of other pharmacological approaches to SCD that are limited by narrow or less powerful mechanisms and therefore may have limited therapeutic benefits. We believe our multidimensional pharmacological approach to the treatment of SCD has the potential to address the multifactorial pathology of this disease.

We believe that olinciguat, by amplifying nitric oxide signaling, has the potential to reduce VOC and chronic symptoms via at least 3 mechanisms



In a preclinical model of SCD, olinciguat treatment was associated with positive effects on key aspects of SCD pathology. The Townes mouse is a knockout-transgenic model of SCD that, like patients with SCD, develops severe hemolytic anemia and organ damage. Male, 9-week-old Townes mice (five mice) treated for 10 days with olinciguat had significantly higher red blood cell counts, total hemoglobin levels and hematocrit (the volume percentage of red blood cells in blood) compared with vehicle-treated controls (five mice), as illustrated in the figure below. In this transgenic mouse model of SCD, olinciguat-treated mice showed a decrease in the progression of hemolytic anemia.

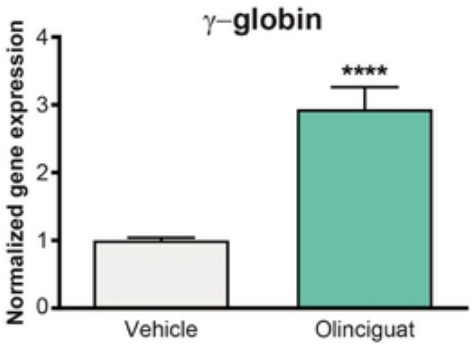
In Townes mouse model of SCD, progression of hemolytic anemia was ameliorated in olinciguat-treated animals



* p<0.05; ** p<0.01 Olinciguat vs Vehicle at Day 10

Induction of HbF has been identified as a mechanism of hydroxyurea in the treatment of SCD and is therefore a clinically validated approach to preventing red blood cell sickling. Because cGMP-mediated signaling is implicated in the regulation of the gene encoding the g-globin subunit of HbF, we believe modulation of nitric oxide signaling has the potential to reduce red blood cell sickling, the underlying pathology of SCD. We evaluated the effects of olinciguat treatment on g-globin mRNA levels in the K562 erythroleukemic cell line. As illustrated below, in cells treated with olinciguat for seven days, the normalized g-globin mRNA expression was almost three-fold greater than that of vehicle-treated control cells. In patients with SCD, higher HbF levels are associated with reduced rates of VOC, decreased frequency of acute chest syndrome and attenuation of other complications of SCD.

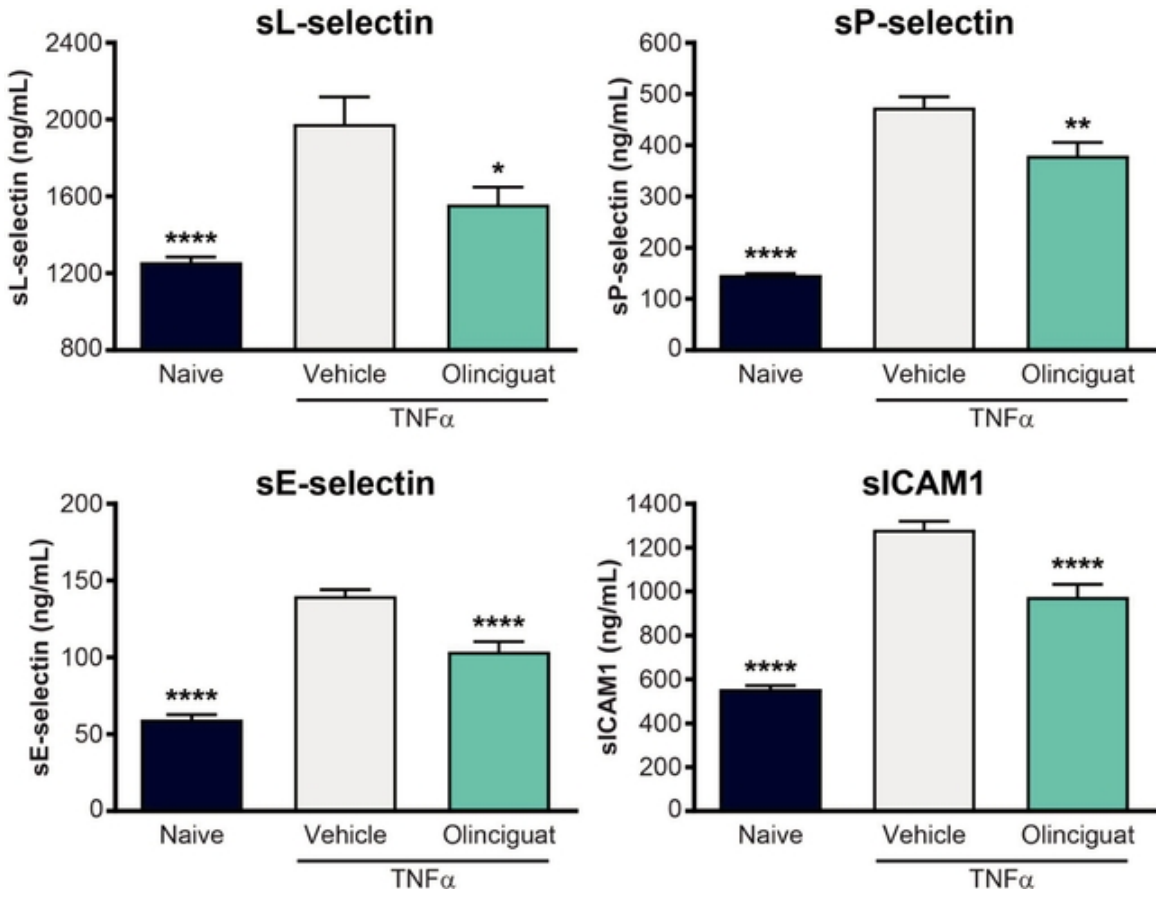
Olinciguat-treated K562 cells, when compared with vehicle-treated cells, had greater normalized mRNA expression of the g-globin subunit of fetal hemoglobin



**** p<0.0001; vs Vehicle

Chronic vascular inflammation in SCD is characterized by the activation of vascular endothelial cells and leukocytes and by the induction of expression of surface adhesion receptors on these cells as well as on platelets. These effects lead to recruitment of sickled red blood cells, leukocytes and platelets to the vascular wall and formation of cell aggregates, which can occlude microcirculation and lead to painful VOCs and other serious complications. Reducing vascular inflammation via blockade of specific adhesion receptors is a validated approach to reduce painful crises in patients with SCD, as demonstrated by a study of the investigational drug crizanlizumab. The effect of olinciguat on the expression of soluble surface adhesion receptors was studied in a mouse model of inflammation in which leukocyte activation is induced by treatment with the pro-inflammatory cytokine TNFa. As shown below, mice (10 mice) pretreated with oral olinciguat one hour before administration of tumor necrosis factor alpha (TNFa) had lower mean plasma levels of the soluble adhesion molecules sL-selectin, sP-selectin, sE-selectin and sICAM-1 than vehicle-treated controls (10 mice), demonstrating attenuation of leukocyte and endothelial cell activation.

In a mouse model of inflammation, leukocyte and endothelial cell activation was attenuated in olinciguat-treated animals



* p<0.05; *** p<0.01; **** p<0.0001 vs TNFa-Vehicle

As a physiological consequence of vascular inflammation and endothelial activation, leukocyte rolling along the vascular wall slows. The speed of leukocyte rolling can be measured in vivo in the vasculature of mice via intravital microscopy. We measured the effect of olinciguat on leukocyte rolling velocity in the venous microcirculation of TNFa-challenged mice. Olinciguat was evaluated both alone and in combination with hydroxyurea, the standard of care in SCD. Treatment of mice with TNFa increased expression of endothelial selectins that form adhesive contacts with leukocytes and slowed leukocyte rolling. Mice pretreated with either olinciguat (three mice) or hydroxyurea (three mice) had significantly faster leukocyte rolling velocities, 10.31±1.14 µm/s (p<0.001) and 15.47±1.68 µm/s (p<0.05), respectively, compared with TNFa controls (three mice), 5.55±0.66 µm/s. The effect was even greater when olinciguat and hydroxyurea were given in combination; leukocyte rolling velocity of combination treatment, 19.66±1.85 µm/s was significantly greater than TNFa controls (p<0.001) and approached the velocity of the naïve controls (three mice), 26.59±3.13 µ m/s. These data demonstrate the functional significance of decreasing vascular inflammation via attenuation of the upregulation of vascular adhesion molecules.

Phase 2 Clinical Study in SCD

We are conducting a Phase 2 study in patients with SCD, the STRONG-SCD study. STRONG-SCD is a randomized, placebo-controlled study in patients evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of three dose levels of olinciguat compared with placebo when administered once daily for 12 weeks. This study is ongoing and enrolling approximately 88 patients aged 16 to 70 years with HbSS, HbSC, $HbSb^0$-thalassemia, or $HbSb^+$-thalassemia and who have experienced one to 10 painful crises in the past year. Patients remain on a stable regimen of their current medication(s) for SCD. Exploratory objectives include evaluation of the effect of olinciguat on painful crisis events, biomarkers of disease activity (*e.g.*, HbF levels, anemia, inflammatory markers) as well as effects on health-related patient-reported outcomes, or PRO, including chronic pain and fatigue. While not explicitly powered for efficacy, we expect to use the data from this trial to evaluate the potential for clinical advancement and, if data warrant, advance the program to a registration trial. We are assessing not only parameters that may allow a direct read on registration endpoints, such as symptoms and pain events, but also parameters that reflect the multidimensional pharmacology we expect to observe based on our preclinical studies. We believe that the full spectrum of data from STRONG-SCD, therefore, will enable us to evaluate potential future clinical development and provide the data to support broad differentiation from other SCD treatments.

The FDA recognizes the importance of patient-focused drug development and has specifically noted that SCD is a disease with significant unmet need, particularly with regard to daily symptoms, such as pain and fatigue. In STRONG-SCD, daily symptoms are being assessed using our Sickle Cell Disease Symptom Assessment Form, or SCD-SAF, a proprietary PRO instrument designed based on patient-centric qualitative research to reflect the most important and relevant symptoms that impact SCD patients. We began developing this PRO instrument before initiating the ongoing Phase 2 trial to enable its use in a registration trial as the assessment underpinning a potential registration endpoint. The SCD-SAF is being developed in accordance with the FDA *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (2009) and good measurement practices. The SCD-SAF is developed from the patient's perspective to measure concepts that are understandable to patients with SCD and include clear instructions and a short recall period. It measures symptom intensity employing well-defined response options that are sufficiently sensitive to detect change. We believe the SCD-SAF will be a fit-for-purpose assessment of treatment benefit in our context of use. In line with our patient-centric approach, we have also established a patient advisory committee to counsel us on our clinical development program to ensure that we are assessing efficacy in a manner that truly meets the needs of patients suffering from SCD. This advisory committee has enhanced our understanding of the daily symptom burden that SCD has on patients and emphasized that relief from those symptoms is important for patients.

Completed Phase 1 Clinical Studies

Phase 1 single-ascending and multiple-ascending dose studies in healthy subjects identified a well-tolerated dose range of once-daily olinciguat, confirmed target engagement and established proof of pharmacology. In these studies of healthy subjects, oral, once-daily olinciguat was well tolerated with no serious adverse events or discontinuations due to adverse events. The most commonly reported adverse events overall in these studies were headache and tachycardia. In the single-ascending-dose study, ICP-1701-101 in 24 subjects, seven of the 18 olinciguat-treated subjects reported headache, three reported tachycardia/sinus tachycardia, three reported nausea and three reported vomiting; all of these events were mild or moderate. No other events were reported in more than two olinciguat-treated subjects. In the multiple-ascending-dose study, ICP-1701-102 in 55 subjects, all five cohorts (8 olinciguat/3 placebo per cohort) were dosed at a single dose level for seven days, and two of the five cohorts up-titrated to a higher dose for seven more days of dosing. During the first seven days of dosing, seven of the 40 olinciguat-treated subjects reported headache, seven reported tachycardia, three

reported hypotension and three reported nausea. In the second seven days of dosing, two of the 16 olinciguat-treated subjects reported headache. All of these events were mild or moderate. No other events were reported in more than two olinciguat-treated subjects. There were no trends of concern in laboratory, electrocardiograph or platelet function parameters in either study. Olinciguat was dose proportional at steady state with a half-life of approximately 30 hours and a low peak-to-trough ratio (<2), a profile that is supportive of once-a-day dosing regimen. Olinciguat demonstrated a moderate volume of distribution (49.4-58.9 L), which is consistent with exposure both in the vasculature and organs, and very low renal clearance (£0.3% of total body clearance) suggesting a low likelihood for dose adjustment in renally impaired patients. Increases in plasma cGMP provided evidence of sGC target engagement, and reduction in blood pressure demonstrated proof of pharmacology.

Market Opportunity

SCD is the most common hemoglobinopathy disorder worldwide. According to the Centers for Disease Control and Prevention, SCD affects approximately 100,000 people in the United States. It is estimated that the prevalence of SCD in the EU5 is 50,000. SCD is a standard part of mandatory newborn screening in the United States, which reveals an incident population of about one in every 365 African-American births and one in every 16,300 Hispanic-American births in the United States. In addition, SCD is estimated to affect approximately 300,000 children born annually worldwide.

SCD is the most prevalent genetic disease in France and the UK, and its frequency is steadily rising in many other countries in Northern, Central and Southern Europe. SCD is particularly common in people whose ancestors come from Sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India and Mediterranean countries such as Greece, Turkey and Italy.

The cost of managing patients with SCD is substantial. The financial burden is largely driven by inpatient admissions; it was shown that the average SCD patient is admitted to the hospital seven times per year with an average length of stay per visit of seven days. Further, a study by Brousseau, et al found that the 30-day rehospitalization rate was 33.4% and nearly 40% of hospital discharges resulted in a 30-day return for acute care, such as a visit to the emergency department. A 2009 study conducted by the Cardeza Foundation at Thomas Jefferson University estimated the average annual cost of managing a patient with HbSS, one of the three major genotypes of SCD, was greater than $230,000, not adjusting for inflation.

Praliciguat for Cardiometabolic Diseases

Praliciguat is an orally administered, once-daily systemic sGC stimulator designed for the treatment of serious cardiometabolic diseases such as DN and HFpEF. In a preclinical study, oral praliciguat demonstrated extensive distribution to adipose, kidney, heart and liver, which we believe is fundamental to its potential to be a breakthrough therapy for cardiometabolic diseases characterized by adipose inflammation and metabolic dysfunction and associated multi-organ etiology and involvement. In addition, in a clinical study, praliciguat showed negligible renal clearance making it well suited to the treatment of patients with cardiometabolic diseases who commonly have compromised renal function. In a Phase 2a study in patients with type 2 diabetes and hypertension (C1973-202, described below), praliciguat-treated patients had greater decreases in blood pressure and glucose and lipid levels compared with placebo-treated patients. We believe these metabolic improvements are particularly notable because all patients in this exploratory study were receiving standard of care therapy for glycemic and blood pressure control, and most were also receiving statins to reduce lipids. Following these positive metabolic results, we initiated our ongoing Phase 2 studies in DN and HFpEF with praliciguat. In addition to establishing proof-of-concept in these serious diseases with high unmet need, we expect to further characterize the metabolic effects of praliciguat in our Phase 2 studies. In September 2018, the FDA designated the investigation of praliciguat for HFpEF as a Fast Track development program.

Diabetic Nephropathy

Disease Background

DN is a common, serious microvascular complication of type 1 and type 2 diabetes mellitus and is characterized by pathological urinary albumin excretion, glomerular lesions, hypertension and progressive loss of renal function. Diagnosis of DN is based on increased albuminuria and/or reduced estimated glomerular filtration rate in patients with diabetes. In patients with diabetes, nephropathy is a major risk factor for cardiovascular disease, the major driver of excess cardiovascular mortality and the single strongest predictor of mortality. DN is progressive, and patients that survive to ESRD require chronic dialysis treatment or kidney transplant.

Current first-line therapy for DN includes glycemic and blood pressure control and treatment with renin-angiotensin-aldosterone system, or RAAS, inhibitors: either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. These treatments may slow the disease, but do not prevent progression to ESRD. In fact, the prevalence of DN has not declined despite increased use of RAAS inhibitors and glucose-lowering medications. Thus, there remains significant unmet medical need for patients with DN.

Nitric Oxide Connection

We believe nitric oxide deficiency plays an important role in the pathogenesis of DN. In the healthy kidney, nitric oxide-sGC-cGMP signaling promotes the relaxation of vascular smooth muscle cells, blocks endothelial cell activation and cytokine-induced injury and inhibits excessive vascular proliferation, fibrosis and inflammation. In patients with diabetes, however, nitric oxide signaling can be impaired due to reduced concentrations of endogenous nitric oxide. Multiple mechanisms contribute to endothelial dysfunction and the reduction in nitric oxide levels in diabetics, including the generation of advanced glycation end-products, increased uric acid levels, increased oxidative stress and increased levels of asymmetric dimethylarginine, or ADMA, which inhibits synthesis of nitric oxide. The resultant decrease in nitric oxide signal may in turn promote the progression of DN. The association between deficient nitric oxide and the development and progression of DN is also established genetically. Multiple genetic polymorphisms in the gene encoding endothelial nitric oxide synthase, or eNOS, a key nitric oxide-producing enzyme in the vasculature, are associated with both DN and reduced enzyme activity or plasma concentrations of nitric oxide.

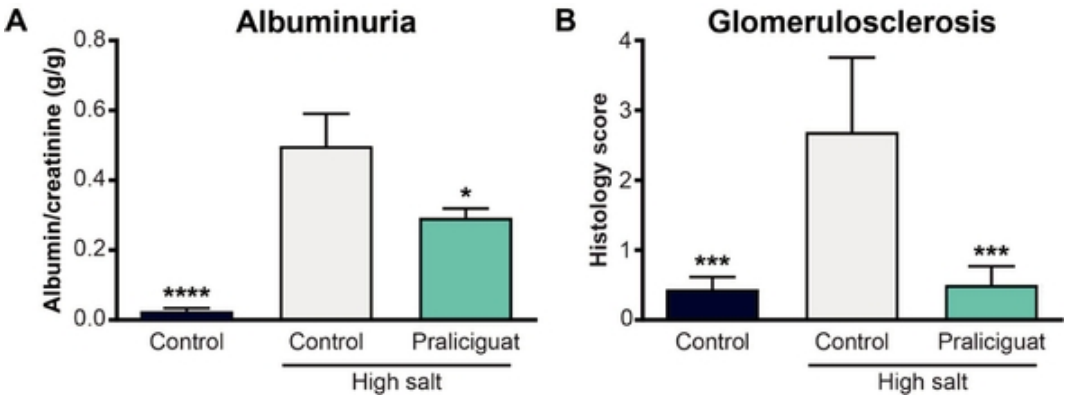
Our Solution

Praliciguat is an oral sGC stimulator that has demonstrated extensive distribution to tissues, including both kidney and adipose, which we believe makes it uniquely suited to treat DN. By acting synergistically with nitric oxide to amplify signaling, we believe praliciguat may compensate for deficits in nitric oxide signaling and ameliorate the pathophysiology of DN. In this way, we believe praliciguat has the potential to improve renal endothelial function, restore appropriate renal blood flow regulation and attenuate or prevent renal inflammation and fibrosis. Based on data from a Phase 2a study (C1973-202, described below) in 26 patients with type 2 diabetes and hypertension, we believe praliciguat may also have positive metabolic effects, including improving insulin sensitivity and LDL cholesterol and triglyceride levels in patients with cardiometabolic disease.

Beneficial effects on renal function were observed in multiple animal models treated with praliciguat, including the ZSF1 and Dahl salt-sensitive rat models. In the obese ZSF1 rat model of DN, plasma, urine and tissue samples were collected at the end of the 11-week study. Obese ZSF1 rats treated with praliciguat (nine rats) had lower liver weight, lower urine volume and proteinuria and lower fasting plasma glucose and cholesterol compared with control animals (eight rats). Moreover, beneficial renal effects were seen at dose levels that had non-significant effects on blood pressure in this study, suggesting the renal-protective effects are independent of systemic hemodynamic effects.

In the Dahl salt-sensitive rat model of hypertension, renal-protective effects were observed in praliciguat-treated animals. Control and treated animals were fed a high-salt diet for eight weeks; after two weeks, praliciguat was added to the high-salt diet of the treated group for the remaining six weeks. Control rats (eight rats) developed kidney damage as evidenced by albuminuria and histological changes. As illustrated below, praliciguat-treated rats (eight rats) had significantly lower levels of urinary albumin than controls (Figure A) suggesting that praliciguat treatment may have blunted the high salt-mediated increase in urinary albumin. Furthermore, histological evaluation of animals treated with praliciguat revealed lower levels of glomerulosclerosis (Figure B) compared with controls. In addition, praliciguat-treated animals had lower level of interstitial fibrosis, interstitial inflammation and vascular alterations compared with controls. Renal-protective effects were observed at a praliciguat dose that produced minimal effects on systemic blood pressure.

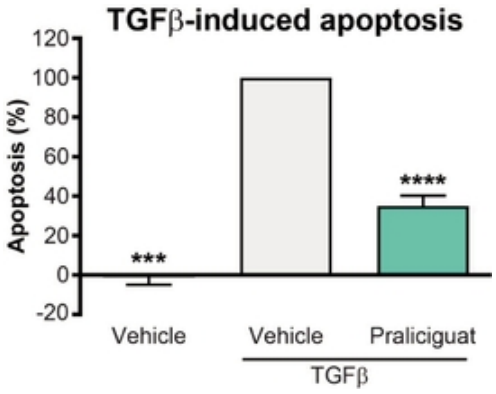
In a preclinical model of hypertension, renal-protective effects were observed in praliciguat-treated animals



* p<0.05; *** p<0.001; **** p<0.0001 vs. High-salt Control

Praliciguat was evaluated in isolated primary human renal proximal tubule epithelial cells (hRPTC) in vitro to mechanistically separate direct effects from effects that may be attributable to changes in local blood flow and hemodynamics. Praliciguat-treated hRPTC cells were inhibited from changing into elongated fibroblast-like cells induced by the profibrotic cytokine, TGFb. As shown in the figure below, praliciguat-treated hRPTC cells also had lower levels of cell death, or apoptosis, induced by treatment with the fibrotic mediator, TGFb, as compared with vehicle-treated cells.

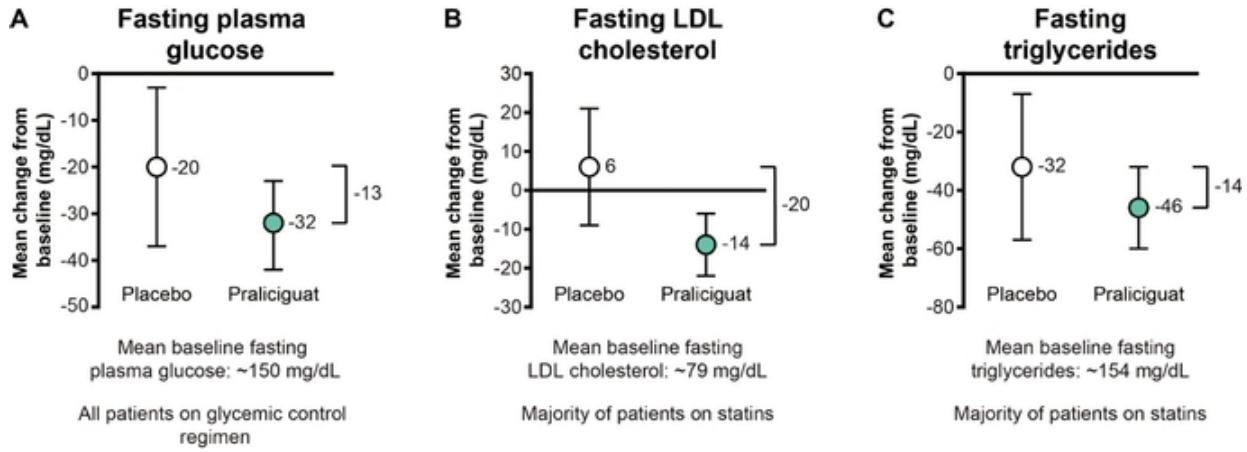
In vitro, praliciguat-treated hRPTC cells had reduced cell death (or apoptosis) triggered by the profibrotic cytokine TGFb



*** p<0.001; **** p<0.0001 vs TGFb-Vehicle

In an exploratory, Phase 2a randomized, placebo-controlled study C1973-202 in 26 patients with type 2 diabetes and hypertension on standard of care therapy, patients treated with praliciguat for 14 days had greater decreases in fasting plasma glucose, LDL cholesterol and triglycerides compared with placebo-treated patients, as shown in Figures A, B and C, respectively. In addition, compared to patients treated with placebo, patients treated with praliciguat had greater decreases in the homeostatic model assessment of insulin resistance, or HOMA-IR, a measure that reflects insulin sensitivity, as well as greater decreases in plasma levels of ADMA, a marker of endothelial dysfunction and cardiovascular disease risk.

In a Phase 2a study, patients with type 2 diabetes and hypertension on standard of care treatment regimen who received praliciguat for two weeks had improvements in multiple metabolic parameters



Phase 2 Clinical Study in Diabetic Nephropathy

We are conducting a dose-ranging Phase 2 trial in DN with the primary efficacy objective of evaluating the effect of praliciguat on urine albumin-to-creatinine ratio, or UACR, an indicator of kidney damage. This randomized, double-blind, placebo-controlled trial is evaluating safety and efficacy of two dose levels of once-daily praliciguat administered for 12 weeks. The study is enrolling approximately 150 adult patients with type 2 diabetes mellitus, albuminuria and impaired renal function who are on stable antihyperglycemic medications and RAAS inhibitors. We have designed this study to enable us to evaluate the potential for clinical advancement following completion of the study.

In addition to UACR, this study is evaluating the effect of praliciguat on hemodynamics measured by ambulatory blood pressure monitoring, cardiovascular and renal biomarkers and metabolic markers, including fasting plasma glucose, lipids, hemoglobin A1c, insulin and insulin resistance. We expect this study will allow us to expand and confirm our understanding of the effects of praliciguat on diabetic, metabolic, vascular and renal parameters, all of which are relevant across diabetic populations. Data are expected in the second half of 2019.

Completed Phase 1 and 2a Clinical Studies

Phase 1 single-ascending and multiple-ascending dose studies in 100 healthy subjects identified a well-tolerated dose range of once-daily praliciguat, confirmed target engagement and established proof of pharmacology. There were no serious adverse events or discontinuations due to adverse events in these studies. In the randomized, placebo-controlled, single-ascending-dose study, ICP-1973-101 in 46 subjects, 11 of the 35 praliciguat-treated subjects reported headache, five reported tachycardia and four reported vomiting. All of these events were mild or moderate except for one adverse event of vomiting that was severe. No other adverse events were reported in more than two praliciguat-treated subjects.

As this was a dose-escalating trial designed to determine the maximum tolerated dose for future clinical trials, most (seven of 11) of the praliciguat-treated subjects who reported headache and all (four of four) of the praliciguat-treated subjects who reported vomiting received dose levels deemed not tolerated in this Phase 1 study. In the randomized, placebo-controlled, multiple-ascending dose study, ICP-1973-102, 44 subjects received a single dose level daily for 14 days then up-titrated to a higher dose for seven more days of dosing. Of the 32 praliciguat-treated subjects, 15 reported headache and six reported dizziness/postural dizziness; all of these events were mild or moderate. No other adverse events were reported by more than two praliciguat-treated subjects. These common adverse events are consistent with the known pharmacology of sGC stimulation and occurred mainly at the higher dose levels. There were no observed trends of concern in laboratory, electrocardiograph or platelet function parameters. Praliciguat exhibited dose-proportional pharmacokinetics with an effective half-life supportive of once-daily dosing. In addition, praliciguat had a large volume of distribution (3100-3610 L) indicating it is broadly distributed to tissues, and negligible renal clearance (£0.01% of total body clearance) suggesting a low likelihood for dose adjustment in renally impaired patients. Increases in plasma cGMP provided evidence of sGC target engagement, and reduction in blood pressure demonstrated proof of pharmacology. In a Phase 1 drug-drug interaction study with aspirin, C1973-103, praliciguat both alone and in combination with aspirin did not affect bleeding time or platelet function in healthy subjects, nor were there any pharmacokinetic interactions between praliciguat and aspirin.

We have also completed two companion exploratory Phase 2a studies in a total of 37 patients with type 2 diabetes and hypertension who were on stable regimens of medications for both diabetes and blood pressure control. The smaller study, C1973-201, was an open-label rapid-dose-escalation study in 11 patients. Praliciguat was well tolerated in this study with four of the eleven patients reporting headache, which were all considered mild; no other adverse events were reported by more than two patients. Study C1973-202 was a randomized, placebo-controlled, 14-day study of once-daily praliciguat in 26 patients. Of the 20 patients who received praliciguat, five each reported headache, hypoglycemia and nausea, and three reported diarrhea; all of these events were considered mild. No other adverse events were reported by more than two patients. A single serious adverse event of upper gastrointestinal hemorrhage deemed severe and study drug related occurred in a patient receiving praliciguat who had ulcerative esophagitis and a previously undiagnosed hiatal hernia; the upper gastrointestinal hemorrhage resolved the same day and the patient recovered completely. There were no observed trends of concern in laboratory, electrocardiograph or platelet function parameters. In these patients on one or more blood pressure-lowering medications, treatment with praliciguat was associated with small but consistent reductions in blood pressure. Patients treated with praliciguat also had positive metabolic changes compared with placebo, including mean declines in fasting plasma glucose, triglycerides and LDL serum cholesterol (see figure above "*In a Phase 2a study, patients with type 2 diabetes and hypertension on standard of care treatment regimen who received praliciguat for two weeks had improvements in multiple metabolic parameters")*. In addition, praliciguat-treated patients had a mean decline in plasma ADMA, a marker of endothelial dysfunction and a risk factor for cardiovascular disease. As in the Phase 1 studies, praliciguat had a large volume of distribution indicating extensive distribution outside the vasculature and a pharmacokinetic/pharmacodynamic profile supportive of once-daily dosing.

Market Opportunity

The World Health Organization estimates that there are over 400 million adults with diabetes globally at a prevalence rate of 8.5%. According to Gheith, et al, up to 40% of all patients with diabetes have DN. The burden of caring for DN patients is high due to the cost of treating ESRD as well as the strong association of DN with cardiovascular morbidity. The total expenses for managing patients with ESRD in 2010 in the United States was $32.9 billion for Medicare patients and $14.5 billion for non-Medicare patients.

HFpEF

Disease Background

Patients with HFpEF have clinical signs and symptoms that include difficulty breathing, shortness of breath while lying down, swelling of the legs, pulmonary congestion and enlargement of the heart. These patients often have low activity levels and impaired quality of life and frequently experience depression. Mortality rates over five years for patients diagnosed with HFpEF have been reported to range from 55% to 74%. Impaired functional capacity is a major source of morbidity in HFpEF patients and substantially affects patients' day-to-day functioning. HFpEF patients generally suffer from multiple co-morbid conditions including type 2 diabetes mellitus, chronic kidney disease, metabolic syndrome, coronary artery disease, obesity and hypertension.

While there have been advances in treatment for patients with heart failure with reduced ejection fraction, or HFrEF, there are no approved therapies to treat HFpEF and treatment options are largely empiric. Lifestyle modifications such as diet and exercise are recommended but are often ineffective. Current management strategies are based on managing the comorbidities that often occur with HFpEF such as diabetes, hypertension, chronic kidney disease, chronic pulmonary disease, obesity and coronary artery disease. Heart failure remains a rising global epidemic with an estimated prevalence of approximately 38 million individuals globally. HFpEF comprises 44% to 72% of new heart failure diagnoses. Patients with HFpEF account for approximately half of the total hospitalizations for heart failure and are frequently re-admitted following discharge.

Nitric Oxide Connection

HFpEF and many of its common comorbid conditions are associated with chronic systemic microvascular inflammation and endothelial dysfunction, which are thought to contribute to the development of cardiac and skeletal muscle inflammation and subsequent fibrosis. In turn, these conditions are accompanied by increased oxidative stress, which reduces nitric oxide signaling and cGMP. Decreased cGMP levels result in multiple downstream effects, including impaired phosphorylation of titin leading to decreased myocardial compliance and increased synthesis of collagen. These effects may further play a role in the reduced ventricular compliance and the myocardial remodeling that is sometimes seen in HFpEF. The resulting endothelial dysfunction also leads to reduced coronary flow reserve and reduced oxygen delivery to, and utilization by, skeletal muscle.

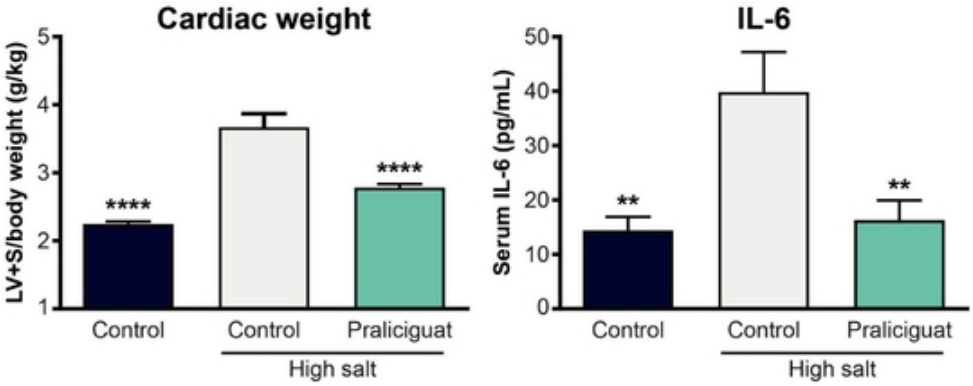
Our Solution

Based on preclinical data, we believe praliciguat has the potential to provide both short- and long-term beneficial effects for patients with HFpEF. By enhancing impaired nitric oxide signaling in the heart and systemic circulation, we believe praliciguat has the potential to improve coronary flow reserve (the maximum increase in blood flow through the coronary arteries above the normal resting volume) as well as oxygen delivery to, and utilization by, skeletal muscle. Through this mechanism, we believe praliciguat may have a positive impact on patient symptoms, including improving exercise tolerance. Furthermore, we believe longer-term treatment with praliciguat has the potential to reduce cardiac stiffness by increasing phosphorylation of titin; to reduce microvascular inflammation and fibrosis, pathophysiological drivers of HFpEF; and to prevent left ventricular remodeling and disease progression. We believe these improvements may translate not only to increases in functional capacity and quality of life for patients with HFpEF, but also to reduction in hospitalizations and mortality in this underserved patient population.

Preclinically, praliciguat treatment was associated with positive effects on cardiac morphology, function and biomarkers in models of heart failure. The Dahl salt-sensitive rat is a model of hypertension that develops cardiac hypertrophy and other characteristics associated with HFpEF. In this

rat model, lower cardiac weight, as well as lower levels of the inflammatory biomarker interleukin 6 (IL-6), was observed in eight rats following six weeks of treatment with praliciguat compared to an untreated control group (eight rats), as shown below.

In a preclinical model of heart failure, lower cardiac hypertrophy and markers of inflammation were observed in praliciguat-treated animals



** p<0.01; **** p<0.0001 vs High-salt Control; LV+S=left ventricular free wall plus ventricular septum

Phase 2 Clinical Study in HFpEF

We are conducting a Phase 2 proof-of-concept trial, CAPACITY-HFpEF, to evaluate the safety and efficacy of once-daily praliciguat over 12 weeks of treatment in approximately 184 patients with HFpEF. The study population is adult patients with established heart failure with an ejection fraction of at least 40%, who demonstrate limited exercise capacity based on cardiopulmonary exercise testing, or CPET, with NYHA class II-IV symptomatology. In addition, patients must have at least two of four risk factors for HFpEF that are associated with decreased nitric oxide signaling: diabetes/prediabetes, hypertension, obesity and advanced age (³70 years). Patients are stratified by atrial fibrillation status and by baseline peak oxygen uptake (VO_2) and randomized to praliciguat or placebo.

The primary efficacy endpoint of this multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study is peak VO_2 measured during CPET. This quantitative measure of exercise capacity defines functional aerobic capacity and reflects a patient's uptake, transport and use of oxygen, which are all aspects that we believe will be improved by the vascular effects of praliciguat. Secondary efficacy endpoints also measure functional capacity and include six-minute walk distance and ventilatory efficiency by CPET. We believe that improvements in these measures may translate into improvements in heart failure prognosis and in a patient's ability to function independently. Additional assessments include echocardiography, NYHA classification and the Kansas City Cardiomyopathy Questionnaire, which assesses health-related quality of life in patients with chronic heart failure. We will also examine biomarkers of metabolic effects, such as lipids, glucose and hemoglobin A1c levels to expand our understanding of the effect of praliciguat on metabolic parameters in patients with HFpEF. Data from this trial are expected in the second half of 2019.

Market Opportunity

Heart failure is the most common cause of hospitalization in Medicare patients and represents 1-2% of all hospitalizations or approximately one million discharges per year. The number of heart failure hospitalization admissions tripled between 1979 and 2004. Between 1987 and 2001, the average prevalence of HFpEF hospitalizations increased from 38% to 54%. Admitted patients with HFpEF have a 50% chance of re-hospitalization for heart failure within six months. Further, total costs for managing heart failure patients in the United States is expected to grow to $53 billion by 2030.

IW-6463 for Neurodegenerative Diseases

IW-6463, which we believe is the first and only sGC stimulator pharmacologically tailored to address neurodegenerative diseases, has demonstrated significant exposure in the CNS in preclinical studies. We believe IW-6463 affords an unprecedented opportunity to expand the utility of sGC pharmacology to serious neurodegenerative diseases. Clinical and nonclinical research suggests that nitric oxide signaling plays a critical role in the CNS in memory formation and retention, cerebral blood flow and neuroinflammation. In preclinical models, IW-6463 treatment was associated with increases in cerebral blood flow; increases in brain tissue cGMP levels; improvements in neuronal health and function; reductions in markers of neuroinflammation; increases in neuroprotective factors, including phosphorylated adenosine 3', 5'-cyclic monophosphate response element-binding protein, or pCREB; and enhanced cognition. CNS pharmacological activity of IW-6463 has been observed preclinically using multiple non-invasive techniques that can also be employed in early clinical studies. Our first-in-human study of IW-6463 initiated in January of 2019 with results expected in the second half of 2019.

Serious Neurodegenerative Diseases Associated with Nitric Oxide Deficiency

Neurodegenerative disease is a comprehensive term for diseases characterized by neuronal death, progressive tissue loss and subsequent mortality. This group of diseases, while widely differing in terms of etiology, genetics, comorbidities and rates of progression, has the common pathophysiology of neuronal damage and cell death and is often associated with deficits in nitric oxide signaling. Disease progression is typically driven by chronic oxidative stress that results in increases in reactive oxygen species and neuroinflammation in the CNS. The persistent inflammatory state leads to decreased neuronal metabolism, impaired blood flow and decreased nutrient supply, all of which ultimately result in loss of neuronal connections, impaired signaling, cell death and cognitive deficits.

We are targeting neurodegenerative diseases that meet the following criteria: (i) serious disease in a precisely defined population where we have potential to offer a breakthrough treatment, (ii) underlying pathophysiology linked to deficiencies in nitric oxide signaling, (iii) ability to demonstrate proof-of-concept in a clear and efficient manner and (iv) opportunity to develop strong value recognized by payors and meaningful commercial potential.

Nitric Oxide Connection

Nitric oxide is a potent neurotransmitter. Increases in nitric oxide signaling have been implicated in promoting neuronal survival and function, restoring vascular tone and regional blood flow and decreasing inflammation and fibrosis. Impaired NO-sGC-cGMP signaling is believed to play an important role in the pathogenesis of several neurodegenerative diseases, and decreased nitric oxide signaling has been linked to cognitive impairment.

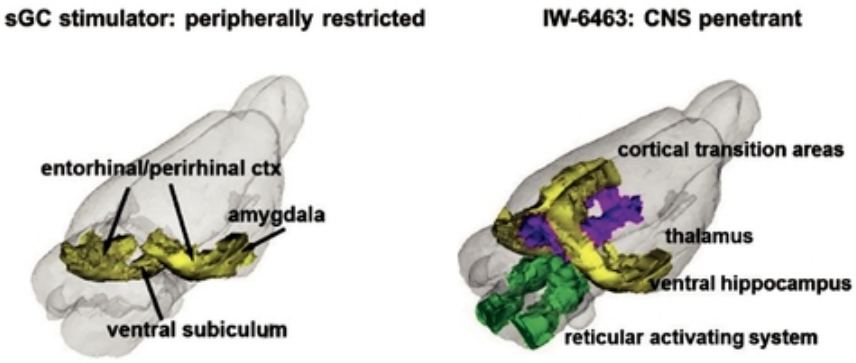
Our Solution

IW-6463 is designed to address serious neurodegenerative diseases through its significant exposure in the CNS. In serious CNS diseases associated with nitric oxide deficiency, we believe IW-6463 may amplify endogenous nitric oxide signaling to alleviate neurodegenerative pathology at the cellular level and thereby restore neuronal health and function. More broadly, in neurodegenerative diseases of varying etiologies, we believe that IW-6463 has the potential to combat neurodegeneration via the neuroprotective and neurofunctional benefits of nitric oxide signaling.

Across a variety of preclinical models, treatment with IW-6463 was associated with increases in cerebral blood flow, reductions in markers of neuroinflammation, increased neuroprotection and enhanced cognition. Furthermore, effects have been demonstrated at doses associated with minimal reductions in systemic blood pressure.

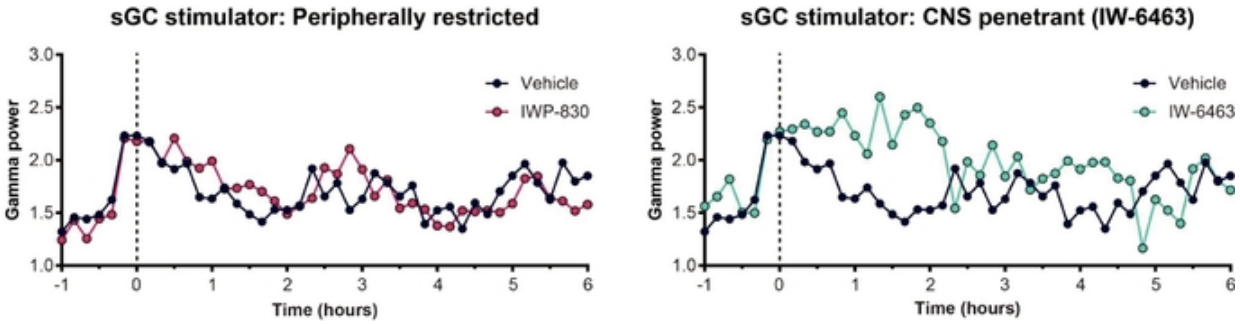
CNS activity can be assessed by measuring blood flow in the brain via functional magnetic resonance imaging using blood-oxygen-level dependent (BOLD) imaging. As shown below, compared with animals treated with a peripherally restricted sGC stimulator that does not penetrate the CNS (left image, eight rats), animals treated with CNS-penetrant IW-6463 (right image, 10 rats) had increased BOLD signal in brain areas associated with memory and arousal in rats, indicating that blood flow to those brain areas increased with IW-6463 treatment.

IW-6463-treated rats had increased blood flow to brain areas associated with memory and arousal relative to rats treated with a peripherally restricted sGC stimulator



Gamma band oscillations as measured by quantitative electroencephalography, or qEEG, are known to be associated with cognitive processing and have been shown to be altered in several neurodegenerative disorders. Cortical activity was measured in rats via qEEG following a single dose of CNS-penetrant IW-6463 (12 rats) or a peripherally restricted sGC stimulator (12 rats). As illustrated in example EEG tracings below, compared with EEG activity in rats receiving the peripherally restricted stimulator, rats receiving IW-6463 had increases in gamma band oscillations demonstrating significant cortical brain activity.

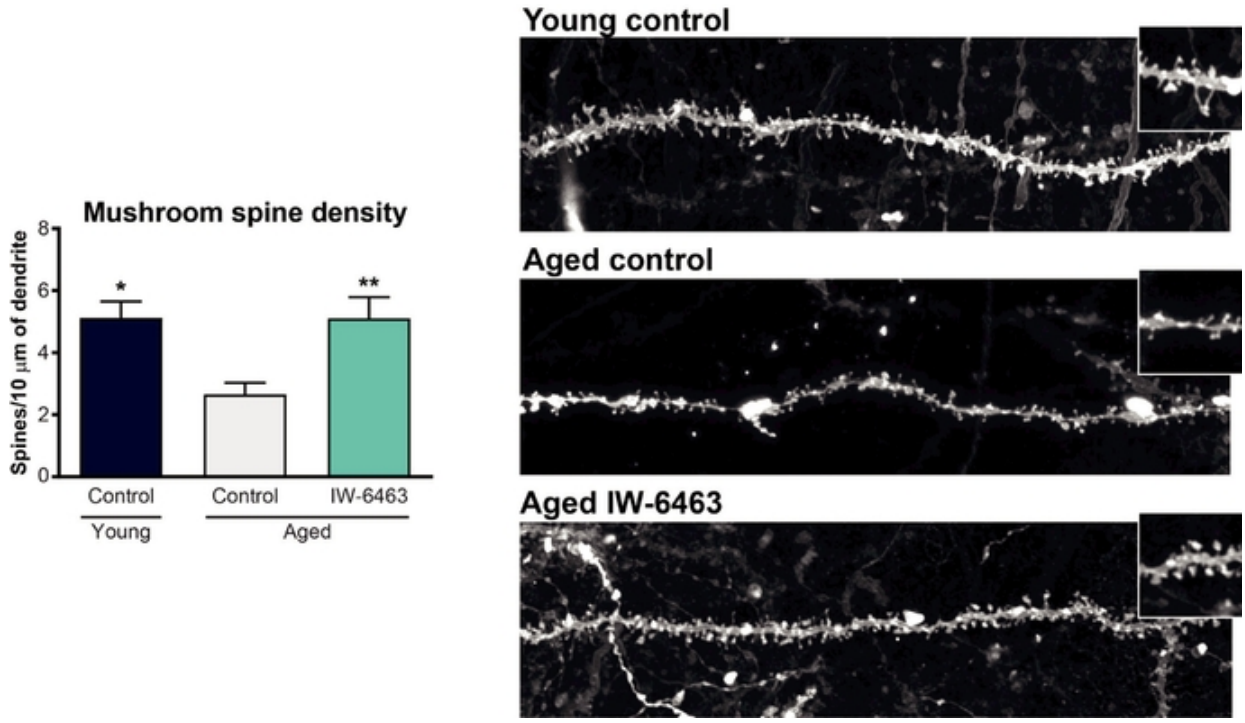
Compared with a peripherally restricted sGC stimulator, cortical brain activity increased in rats following single-dose IW-6463



Dendritic spines protrude from the dendritic shafts of neurons and are involved in the synaptic processes that underlie cognitive function. Loss of neuronal spines is associated with neurogenerative disorders, is correlated with decreased synaptic function and may contribute to cognitive dysfunction. We evaluated the effects of IW-6463 on the density of spines of pyramidal neurons in the hippocampus of aged mice. As illustrated below, after four months of treatment, the density of hippocampal neuronal spines in IW-6463-treated aged mice was not only greater than that of vehicle-treated aged mice controls but was at the same level as that of the young control mice (six mice per group with five

sections per mouse). Restoration of spine density has the potential to provide neuroprotective effects and improve synaptic function in neurodegenerative diseases.

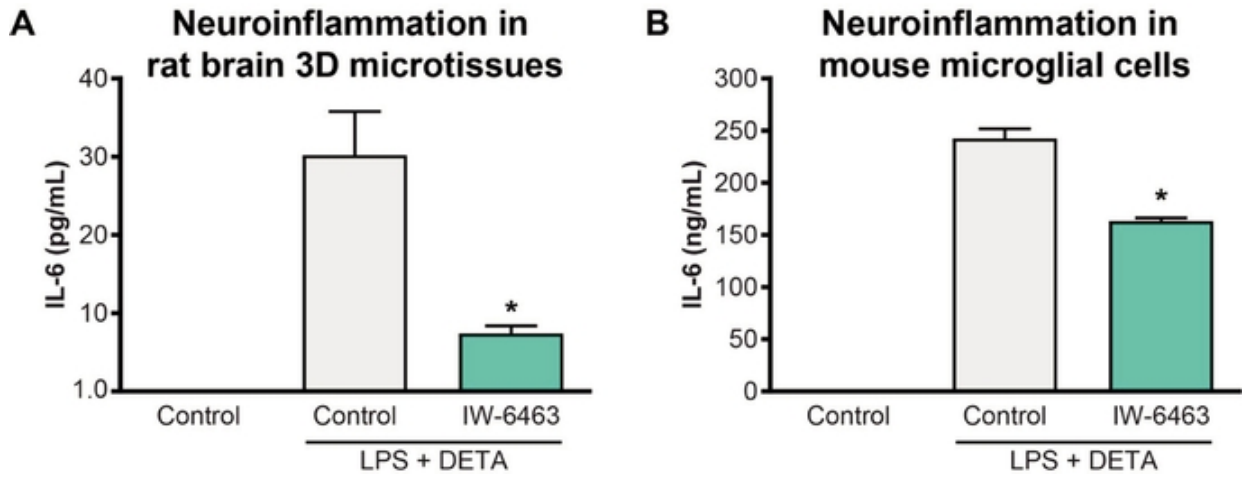
Aged mice treated with IW-6463 for four months had neuronal spine density greater than that observed in aged control mice and similar to that observed in young control mice



* p<0.05 vs Aged control

Inflammation in the CNS drives the progression of neurodegeneration by multiple mechanisms, including disruption of healthy neuronal processes and blood-brain barrier integrity, which are critical to homeostasis of the CNS. The effects of IW-6463 on markers of inflammation were studied in two in vitro models. In the first, the effect of IW-6463 was studied in rat brain 3D microtissues, a 3D cell model containing a mix of neurons, astrocytes, microglial cells and oligodendrocytes. In this in vitro model, brain microtissues pretreated with IW-6463 had lower levels of lipopolysaccharides (LPS)-induced inflammatory cytokines and pro-apoptotic markers, including IL-6, compared with control, as shown in Figure A below. In a second in vitro study, mouse microglial SIM-A9 cells pretreated with IW-6463 had lower levels of LPS-induced IL-6 compared with control, as shown in Figure B below. We believe these results suggest that IW-6463 has the potential to inhibit neuroinflammation, thus promoting neuronal survival.

In rat brain 3D microtissues and mouse microglial cells, IW-6463 pretreatment was associated with reduced LPS-induced proinflammatory cytokines

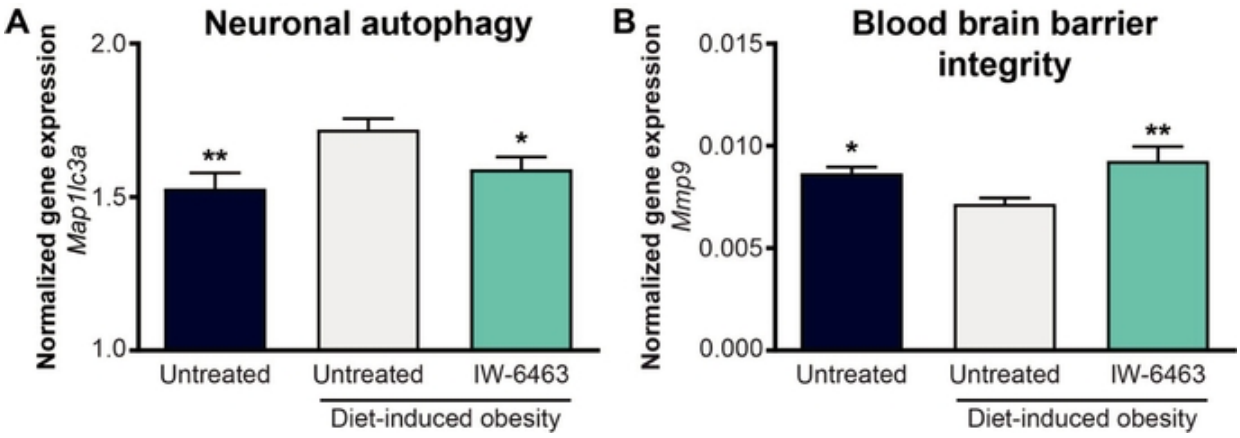


* p<0.05 vs LPS + DETA Control.

NOTE: Values for the non-LPS-induced Control were below the limit of quantification and not included in the statistical analysis.

Neuroinflammation accompanies obesity-related metabolic diseases, which are in turn associated with multiple neurogenerative diseases. To assess the effects of IW-6463 on obesity-induced neuroinflammatory-associated processes, we studied markers of neuronal health in the diet-induced obesity mouse model. We measured gene expression of microtubule-associated protein 1-light chain 3A, or Map1lc3a, a marker for autophagy. Neuronal autophagy is a cellular degradation process necessary for the maintenance of neuronal function, and impaired autophagy leads to neurodegeneration. As illustrated below in Figure A, obese mice (nine mice) treated with IW-6463 had lower levels of Map1lc3a in the hypothalamus compared with those untreated (nine mice). We also assessed the effect of IW-6463 on blood-brain barrier integrity in this model via gene expression of matrix metalloproteinase 9, or MMP-9, as decreases in MMP-9 expression are associated with neuronal cell loss. As illustrated below in Figure B, IW-6463-treated obese mice had higher expression levels of MMP-9 compared with untreated obese mice. We believe these results demonstrate neuroprotective effects that are a functional consequence of anti-inflammatory activity in the CNS.

IW-6463 treatment was associated with anti-inflammatory neuroprotective effects in the mouse obesity model

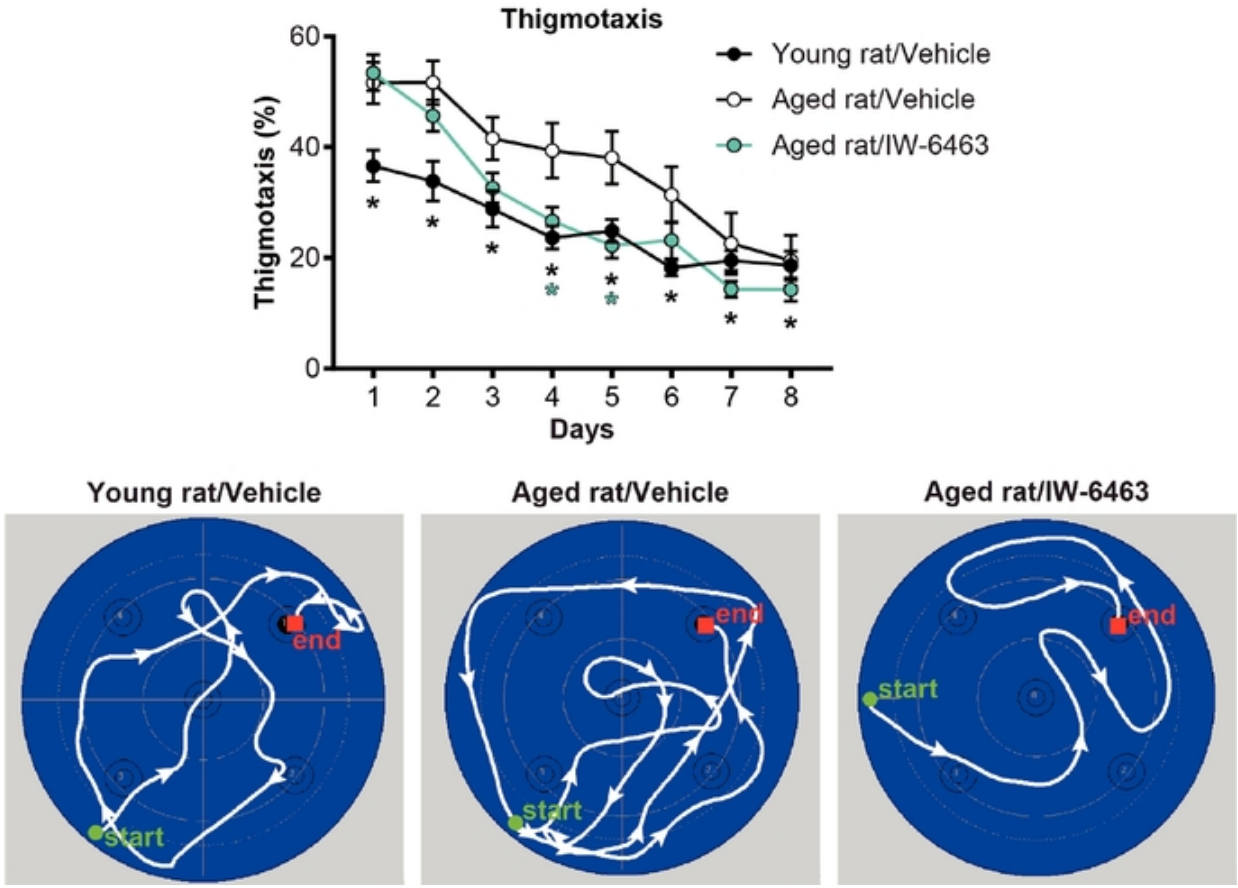


* p<0.05;

** p<0.01 vs Obese Control

IW-6463 treatment was also associated with positive cognitive effects in multiple animal models, including both aged and pharmacologically impaired rats. The effects of daily oral IW-6463 treatment in aged rats were assessed over eight days in the Morris water maze, a test of spatial and learning memory. On Day 1, thigmotaxis (wall-following behavior that delays maze solving) was similar in aged animals receiving IW-6463 (18 rats) and aged animals receiving vehicle (17 rats), while young animals receiving vehicle (20 rats) had lower values as depicted in the figure below. As exemplified by the path tracings, on days 4 and 5, IW-6463-treated rats had a mean thigmotaxis value lower than that of aged vehicle-treated rats, and similar to that of young vehicle-treated rats.

IW-6463-treated aged rats had improvements in thigmotaxis compared with vehicle-treated aged rats



* p<0.05; vs Aged/Vehicle

Based on these preclinical data indicating that IW-6463 treatment was associated with increased cerebral blood, flow, decreased neuroinflammation, increased neuroprotection and improved synaptic and cognitive function, we believe that IW-6463 provides a unique opportunity for the potential treatment of neurodegenerative diseases characterized by progressive neuronal dysfunction and neuronal loss that result in cognitive impairment. By amplifying nitric oxide signaling in the brain, we believe IW-6463 has the potential to simultaneously address multiple facets of neurodegeneration and alter or modify the course of disease.

Clinical Development

IW-6463 is being evaluated in a first-in-human study that initiated in January 2019 with results expected in the second half of 2019. Our Phase 1 study is not only designed to provide safety, tolerability and pharmacokinetic data on single- and multiple-ascending doses of IW-6463, but also to potentially translate our observed preclinical effects to humans, demonstrating proof of pharmacology. We will evaluate the effects of IW-6463 by using quantitative, objective measures of brain activity, such as qEEG, and a select battery of well-characterized cognitive and motor assessments. After Phase 1, we plan to conduct early proof-of-concept studies in well-defined populations with neurological deficits mechanistically linked to nitric oxide signaling. This stepwise approach provides the opportunity to attain an initial clinical read on the potential of this mechanism to treat neurodegenerative diseases.

Organ-targeted sGC Stimulators in Late Discovery

sGC stimulation is a powerful mechanism that can broadly regulate blood flow, inflammation, fibrosis and metabolism. In diseases that are localized to specific organs or tissues, we believe that our organ-targeting strategy will maximize the efficacy of sGC pharmacology in key organs while reducing the potential for dose-limiting hemodynamic effects sometimes observed with sGC stimulation. Our initial focus is on the liver and the lung due to the clear role of nitric oxide signaling in diseases with high unmet need that affect these organs. We currently have two late stage discovery programs focusing on delivery of a liver-targeted compound for serious and orphan hepatic diseases and a lung-targeted compound for serious and orphan pulmonary diseases.

Liver-targeted sGC Stimulators

In animal models of liver fibrosis treated with systemic sGC stimulators, we have observed reductions in liver fibrosis, inflammation and steatosis, pathophysiological processes that underlie multiple chronic liver diseases. Our solution for these diseases is to modulate the physicochemical properties of a sGC stimulator to target the liver while minimizing systemic exposure. We have developed orally administered sGC stimulators that are designed to selectively partition to the liver to achieve tissue concentrations that are greater than 20-fold higher than corresponding plasma concentrations. Selectivity for liver tissues over plasma is intended to allow us to maximize hepatic pharmacology. We expect to nominate a development candidate in the second quarter of 2019 and file an IND and/or CTA application thereafter. We believe this new oral sGC stimulator will allow us to fully exploit the potential of nitric oxide signaling pharmacology to treat serious liver diseases.

Lung-targeted sGC Stimulators

Our lung-targeted program is aimed at realizing the full potential of sGC stimulation in pulmonary diseases, by selectively increasing exposure in the lung. We designed lung-retentive, lung-stable sGC stimulators that are delivered via pulmonary administration. Our lead molecule is highly retained in the lung with greater than 50-fold selectivity for lung over plasma in an animal model. In addition, while our lung-targeted stimulator is metabolically stable in the lung, it is unstable in the plasma with rapid systemic clearance. This targeting strategy is intended to maximize the efficacy of sGC pharmacology in the lung while reducing potential dose-limiting systemic effects sometimes observed with sGC stimulation. We are pursuing the identification of a development candidate, and expect to progress to filing an IND/CTA, thereafter.

Intellectual Property

We vigorously protect the intellectual property and proprietary technology that we believe is important to our business, including by pursuing and maintaining U.S. and foreign patents that cover our products and compositions, their methods of use and the processes for their preparation, as well as any other relevant inventions and improvements that are commercially important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our commercial success depends in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions, improvements and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties.

As of April 2, 2019, we had 10 issued U.S. patents, 21 pending U.S. patents applications, eight pending Patent Cooperation Treaty, or PCT, applications, and numerous foreign patents and pending patent applications. The PCT applications are filed under the PCT, an international patent law treaty that provides a unified procedure for filing a single initial patent application to seek patent protection for an invention simultaneously in each of the 152-member states, followed by the process of entering national phase, which requires a separate application in each of the member states in which national patent protection is sought.

The technology underlying our sGC patents and pending patent applications has been developed by us and was not acquired from any in-licensing agreement. We own all of the issued patents and pending applications.

The intellectual property portfolios for our most advanced product candidates as of April 2, 2019, are summarized below.

Olinciguat Patent Portfolio

Our olinciguat patent portfolio in the U.S. includes three U.S. patents, six pending U.S. patent applications and two PCT applications.

One of the U.S. patents, US 9,586,937, which will expire in 2034, is directed to olinciguat and pharmaceutical compositions thereof. The term of this U.S. patent may be eligible for patent term extension as described below. The other two U.S. patents, US 8,748,442 and US 9,139,564, expire in 2031, and provide generic coverage of olinciguat and intermediates used in the preparation of olinciguat, respectively.

We have a pending U.S. application directed to methods of treating SCD with olinciguat, that, if issued, will expire in 2034 or later. Methods of treating other diseases with olinciguat are disclosed in pending PCT and U.S. applications, that if issued, will expire in 2036 or later. We have pending PCT and U.S. applications directed to polymorphs of olinciguat and processes and synthetic intermediates for preparing olinciguat that, if issued, will expire in 2037 or later.

Furthermore, we have two granted European patents, one expiring in 2031 and the other in 2032; two granted Japanese patents, one expiring in 2031 and the other in 2034; two granted Chinese patents, one expiring in 2031 and the other in 2032; and seven issued patents in other foreign jurisdictions, all expiring in 2031. Some of these patents may be eligible for patent term extension depending on the jurisdiction. We also have numerous patent applications pending in foreign jurisdictions.

Praliciguat Patent Portfolio

Our praliciguat patent portfolio in the U.S. includes four U.S. patents, seven pending U.S. patent applications and two PCT applications.

One of the U.S. patents, US 9,481,689, which will expire in 2034, is directed to praliciguat and pharmaceutical compositions thereof. The term of this U.S. patent may be eligible for patent term extension as described below. Two other U.S. patents, US 8,748,442 and US 9,139,564, expire in 2031, and provide generic coverage of praliciguat and intermediates used in the preparation of praliciguat, respectively. The fourth U.S. patent, US 10,183,021 will expire in 2034 and is directed to the treatment of resistant hypertension with praliciguat or combinations of praliciguat and known anti-hypertensives.

We have a pending U.S. application directed to a method of treating DN with praliciguat, that, if issued, will expire in 2034 or later. We have pending PCT and U.S. applications directed to methods of treating other diseases with praliciguat, that if issued, will expire in 2036 or later. We intend to pursue claims to a method of treatment of heart failure with praliciguat at a later date.

We have a pending U.S. application directed to a praliciguat formulation, that, if issued, will expire in 2036 or later. We have a pending PCT and a pending U.S. application directed to processes and synthetic intermediates for preparing praliciguat that, if issued, will expire in 2037 or later.

Furthermore, we have two granted European patents, one expiring in 2031 and the other in 2032; two granted Japanese patents, one expiring in 2031 and the other in 2034; three granted Chinese patents, one expiring in 2031, one in 2032, and the third expiring in 2034; and nine issued patents in other foreign jurisdictions, seven of them expiring in 2031 and two expiring in 2034. Some of these patents may be eligible for patent term extension depending on the jurisdiction. We also have numerous patent applications pending in foreign jurisdictions.

IW-6463 Patent Portfolio

Our patent estate includes pending PCT, U.S. and foreign applications directed to IW-6463, pharmaceutical compositions thereof, and methods of treating several types of neurodegenerative diseases, that, if issued, will expire in 2037 or later.

Additional Intellectual Property

In addition to the patents and patent applications related to praliciguat, olinciguat and IW-6463, we currently have five issued U.S. patents; nine patents granted in foreign jurisdictions, including European patents that have each been validated in several countries; and a number of pending U.S., foreign and PCT applications directed to other sGC stimulator molecules and uses thereof.

Patent Term

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application, assuming that all applicable maintenance or annuity fees are paid. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO, in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. However, the actual protection afforded by a patent varies on a product by product basis, from country to country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in that country, and the validity and enforceability of the patent.

In addition, the term of a U.S. patent that covers an FDA-approved drug may be eligible for patent term extension under the Drug Price Competition and Hatch-Waxman Act, to account for some of the time the drug is under development and regulatory review after the patent is granted. For a drug for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of the term of one U.S. patent that includes at least one claim covering the composition of matter of an FDA-approved drug, an FDA-approved method of treatment using the drug and/or a method of manufacturing the FDA-approved drug. The extended patent term cannot exceed the shorter of five years beyond the non-extended expiration of the patent or 14 years from the date of the FDA approval of the drug. Some foreign jurisdictions, including Europe and Japan, have similar patent term extension provisions, which allow for extension of the term of a patent that covers a drug approved by the applicable foreign regulatory agency.

Trade Secrets and Proprietary Information

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We typically rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. We protect our proprietary information, including trade secrets and know-how, by establishing confidentiality agreements with our commercial partners, collaborators, scientific advisors, employees and consultants and invention assignment agreements with our employees, consultants, scientific advisors and contractors. These agreements generally provide that all confidential information developed or made known during the course of an individual or entities' relationship with us must be kept confidential during and after the relationship. These agreements also typically provide that all inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. However, these agreements may be breached, and we may not have adequate remedies for any breach. We also take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary information by third parties. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Government Regulation

In the United States, the FDA regulates medical products, including prescription drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and its implementing regulations. Products are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including imposition of a clinical hold, refusal by the FDA to approve applications, withdrawal of an approval, import/export delays, issuance of warning letters and other types of enforcement letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA, the Department of Justice, State Attorneys General, or other governmental entities.

The process required by the FDA before a drug may be approved and marketed in the United States generally involves the following:

- completion of extensive pre-clinical laboratory tests and animal tests conducted in accordance with applicable regulations, including Good Laboratory Practices, or GLP, regulations and applicable requirements for the humane use of laboratory animals;

- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may commence;

- approval by an independent IRB, representing each clinical site before each clinical trial may be initiated;

- performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, GCPs and other clinical-trial related regulations to establish the safety and efficacy of the product for each proposed indication;

- preparation and submission to the FDA of a NDA;

- satisfactory completion of one or more FDA pre-approval inspection(s) of the manufacturing facility or facilities at which the product, or components thereof, are made to assess compliance with current GMP;

- payment of user fees for FDA review of the NDA; and

- FDA acceptance, review and approval of the NDA, which may include an Advisory Committee review.

The development and approval process require substantial time, effort and financial resources and the receipt and timing of any approval is uncertain.

Preclinical and Human Clinical Trials in Support of an NDA

Before testing any drug product candidate in humans, the product candidate must undergo rigorous pre-clinical testing. Pre-clinical studies include laboratory evaluations of the product candidate, as well as in vitro and animal studies to assess the potential safety and efficacy of the product candidate. The conduct of pre-clinical trials must comply with federal regulations and requirements, including GLP regulations. The sponsor must submit the results of the pre-clinical studies, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND, which must become effective before clinical trials may be commenced. The IND will become effective automatically 30 days after receipt by the FDA, unless the FDA raises concerns or questions about the conduct of the trials as outlined in the IND prior to that time. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed.

Clinical trials involve the administration of the product candidate to human subjects under the supervision of qualified investigators in accordance with GCP requirements. Each clinical trial must be reviewed and approved by an IRB for the sites at which the trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution. The IRB also approves the informed consent form, including a privacy statement, that must be provided to each clinical trial subject or his or her legal representative, and must monitor the clinical trial until completed.

Clinical trials are typically conducted in three sequential phases prior to approval, which may overlap or be combined:

- *Phase 1.* Phase 1 clinical trials generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.

- *Phase 2.* Phase 2 clinical trials usually involve studies in a limited patient population to evaluate the efficacy of the product candidate for specific indications, determine dosage tolerance and optimal dosage and identify possible adverse effects and safety risks.

- *Phase 3.* Phase 3 clinical trials generally involve a larger number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for

its intended use, its safety in use, to establish the overall benefit/risk profile of the product and to provide an adequate basis for product approval.

- *Phase 4.* Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be required to be conducted after approval to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of drugs approved under accelerated approval regulations, or when otherwise requested by the FDA. Failure to promptly conduct any Phase 4 clinical trials required by the FDA could result in enforcement action or withdrawal of approval.

Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. The FDA or the sponsor may suspend or terminate a clinical trial at any time, or the FDA may impose other sanctions on various grounds, including a finding that the research patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the requirements of the IRB or if the drug has been associated with unexpected serious harm to patients. There are also requirements related to registration and reporting of certain clinical trials and completed clinical trial results to public registries.

Submission and Review of an NDA

Assuming successful completion of the required pre-clinical and clinical testing, the results of pre-clinical studies and clinical trials, together with detailed information on the product's manufacture, composition, quality controls and proposed labeling, among other things, are submitted to the FDA in the form of an NDA, requesting approval to market the product for one or more indications. The application must be accompanied by a significant user fee payment, which typically increases annually, although waivers may be granted in limited cases (*e.g.*, for products that have received an Orphan Designation).

As an alternative path to FDA approval for modifications to formulations or uses of drugs previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. In contrast to the traditional NDA, which requires submission of a full slate of pre-clinical and clinical data, a Section 505(b)(2) NDA can rely, at least partially, on data from studies not conducted by, or for, the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

The FDA has substantial discretion in the approval process and may refuse to accept any application or decide that the data is insufficient for approval, and may require additional preclinical, clinical or other studies before it accepts the filing. If an NDA has been accepted for filing, which occurs 60 days after submission, the FDA sets a user fee goal date that informs the applicant of the specific date by which the FDA intends to complete its review. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original NDAs, the FDA has ten months from the filing date in which to complete its review of a standard application, and six months from the filing date for an application with priority review. The FDA does not always meet its PDUFA goal dates, and the review process may be significantly extended by FDA requests for additional information and clinical data or clarification.

The FDA reviews NDAs to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with current GMP to assure and preserve the product's identity, strength, quality and purity. Before approving an NDA, the FDA typically will inspect the facilities at which the product is manufactured and will not approve the product unless the manufacturing facilities comply with current GMP. Additionally, the FDA will frequently inspect one or more clinical trial sites for compliance with GCPs and integrity of the data supporting safety and efficacy.

During the approval process, the FDA will also prepare an integrated benefit risk assessment and determine whether a Risk Evaluation and Management plan, or REMS, is necessary to ensure that the benefits of the drug outweigh the risks and to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the application must submit a proposed REMS. A REMS that includes elements to assure safe use, or ETASU, can substantially increase the costs of commercializing a drug. The FDA could also require a special warning, known as a boxed warning, to be included in the product label in order to highlight a particular safety risk. Boxed warnings may limit the type of advertising for a drug. The FDA may also convene an advisory committee of external experts to provide input on certain review issues relating to risk, benefit and interpretation of clinical trial data.

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, FDA will issue either an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug and is accompanied by specific prescribing information for specific conditions of use. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter usually describes all of the specific deficiencies in the submission identified by the FDA and may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either amend the NDA with data to address the raised concerns, resubmit the NDA, addressing all the deficiencies identified in the letter, engage in dispute resolution with the FDA about the identified deficiencies in the CRL, or withdraw the application. Even with submission of this additional information, the FDA may ultimately decide that the re-submitted application does not satisfy the regulatory criteria for approval.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the United States, or in other limited cases. Orphan drug designation must be requested before submitting an NDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, though companies developing orphan drugs may be eligible for certain incentives, including tax credits for qualified clinical testing. In June 2018, the FDA granted orphan drug designation to our product candidate olinciguat for the treatment of patients with SCD.

Generally, if a product that has orphan drug designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same active moiety for the same indication for seven years from the date of such approval, except in limited circumstances. Competitors, however, may receive approval of different active moieties for the same indication or obtain approval for the same active moiety for a different indication. If one of our products designated as an orphan drug receives marketing approval for an indication broader than that which is designated, it may not be entitled to orphan drug exclusivity.

Expedited Review and Approval

The FDA has various programs that are intended to expedite development and approval of drugs intended for the treatment of serious or life-threatening diseases or conditions and that demonstrate the potential to address unmet medical needs.

An application may be eligible for a "fast track" designation for a product that is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. Fast track designation provides opportunities for more frequent interactions with the

FDA review team and permits FDA to consider sections of the NDA on a rolling basis before the complete application is submitted. In September 2018, the FDA granted fast track designation to our product candidate praliciguat for the treatment of patients with HFpEF.

In addition, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The FDA must take certain actions with respect to breakthrough therapies, such as holding timely meetings with and providing advice to the product sponsor.

An application may be eligible for "accelerated approval" where the product candidate is intended to treat a serious or life-threatening illness and provides meaningful therapeutic benefit over existing treatments; applications eligible for accelerated approval may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA requires a sponsor to conduct confirmatory studies to verify the predicted effect on IMM or another clinical endpoint, and the product may be subject to expedited withdrawal procedures.

Once an NDA is submitted for a product intended to treat a serious condition, the FDA may assign a priority review designation if the FDA determines that the product, if approved, would provide a significant improvement in safety or effectiveness. Under priority review, the FDA must review an application in six months, compared to ten months for a standard review. A product may be eligible for more than one expedited approval program. Even if a product qualifies for one or more of these programs, however, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Furthermore, these expedited review pathways do not change the standards for approval and may not ultimately expedite the development or approval process.

Non-Patent Exclusivity

In addition to patent exclusivity, the holder of the NDA for the listed drug may be entitled to a period of non-patent exclusivity, during which the FDA cannot approve an ANDA for approval of a generic or 505(b)(2) application that relies on the listed drug as protected by regulatory exclusivity.

An NDA for a new chemical entity may receive five years of exclusivity, whereby the FDA will not accept for filing, with limited exceptions, a product seeking to rely upon the FDA's findings of safety or effectiveness for such new chemical entity. An ANDA containing a paragraph IV patent certification can be filed after four years. Alternatively, an NDA may obtain a three-year period of non-patent market exclusivity for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity for both drugs and biologics, and also Orange Book listed patents in the case of drugs. This six-month exclusivity may be granted if a sponsor submits pediatric data that

fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted.

Orange Book Listing

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product or an approved method of using the product. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, known as the Orange Book. Any applicant who files an ANDA seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must certify, for each patent listed in the Orange Book for the referenced drug, to the FDA that (i) no patent information on the drug product that is the subject of the application has been submitted to the FDA, (ii) such patent has expired, (iii) if such patent has not expired, the date on which it expires or (iv) such patent is invalid, unenforceable, or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. The fourth certification described above is known as a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA or 505(b)(2) application refers. The applicant may also elect to submit a "section viii" statement certifying that its proposed label does not contain (or carves out) any language regarding the patented method-of- use rather than certify to a listed method-of-use patent. This section viii statement does not require notice to the patent holder or NDA owner. There might also be no relevant patent certification.

If the reference NDA holder and patent owners assert a patent challenge directed to one of the Orange Book listed patents within 45 days of the receipt of the paragraph IV certification notice, the FDA is prohibited from approving the ANDA until the earlier of 30 months from the receipt of the paragraph IV certification, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the applicant. If the 45-day period expires without a patent infringement lawsuit being commenced against the applicant, a lawsuit can still be brought and could delay market entry, but such lawsuit would not initiate the 30-month stay of FDA approval.

The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired as described above.

Post-Approval Requirements

Following approval of a new product, the manufacturer and the approved product are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims and some manufacturing and supplier changes, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for marketed products and the establishments where such products are manufactured, as well as new application fees for certain supplemental applications. The FDA may impose a number of post-approval requirements as a condition of approval of an NDA, such as Phase 4 clinical trials or a REMS.

In addition, entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and such state agencies for compliance with current GMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA

approval before being implemented. FDA regulations also require investigation and correction of any deviations from current GMP requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain current GMP compliance.

Once an approval is granted, the FDA may issue enforcement letters or withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Corrective action could delay product distribution and require significant time and financial expenditures. Later discovery of previously unknown safety issues with a product, including adverse events of unanticipated severity or frequency, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or other enforcement-related letters of clinical holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- injunctions or the imposition of civil or criminal penalties; and
- consent decrees, corporate integrity agreements, debarment, or exclusion from federal healthcare programs.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications, in accordance with the provisions of the approved label and FDA guidance. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability, including investigation by federal and state authorities. Additionally, all promotional material must be truthful and non-misleading, and present balanced information regarding the risks and benefits of the drug product.

Review and Approval of New Drug Products in the European Union

In the European Union, medicinal products are subject to extensive pre- and post-market regulation by regulatory authorities at both the European Union and national levels. There may be local legislation in various European Union Member States, which may be more restrictive than the European Union legislation, and we would need to comply with such legislation to the extent it applies.

Clinical Trials

Clinical trials of medicinal products in the European Union must be conducted in accordance with European Union and national regulations and the International Conference on Harmonization, or ICH, guidelines on GCPs. The sponsor must take out a clinical trial insurance policy, and in most European Union countries, the sponsor is liable to provide "no fault" compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the competent authority, and a positive opinion from an independent EC. The application for a clinical

trial authorization must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, clinical trial authorization applications must be submitted to the competent authority in each EU Member State in which the trial will be conducted.

Under the new Regulation on Clinical Trials, which is currently expected to take effect in 2019, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the CTAs must be notified to or approved by the relevant competent authorities and ECs. Medicines used in clinical trials must be manufactured in accordance with cGMP. Other national and European Union-wide regulatory requirements also apply.

During the development of a medicinal product, the EMA and national medicines regulators within the European Union provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use, or CHMP. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Given the current stage of the development of our product candidates, we have not yet sought any such advice from the EMA. However, to the extent that we do obtain such scientific advice in the future, such advice will, in accordance with the EMA's policy, not be legally binding on the EMA and the European Commission, and the European Commission may still not approve any future marketing authorization application, or MAA, of the product concerned even if we followed the scientific advice received by the CHMP.

Marketing Authorizations

In order to market a new medicinal product in the European Union, a company must submit and obtain approval from regulators of a MAA. The process for doing this depends, among other things, on the nature of the medicinal product.

The centralized procedure results in a single marketing authorization, or MA, granted by the European Commission that is valid across the EEA (*i.e.*, the European Union as well as Iceland, Liechtenstein and Norway). The centralized procedure is compulsory for medicinal products for human use that are: (i) derived from certain biotechnology processes, such as genetic engineering, (ii) contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions and viral diseases, (iii) officially designated orphan medicines and (iv) advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The centralized procedure may at the request of the applicant also be used in certain other cases.

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA by the EMA is 210 days. This excludes so-called clock stops, during which additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. At the end of the review period, the CHMP provides an opinion to the European Commission. If this opinion is favorable, the Commission may then adopt a decision to grant an MA. In exceptional cases, the CHMP might perform an accelerated review of an MAA in no more than 150 days. This is usually when the product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation.

The European Commission may grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines

designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (iii) the product fulfills an unmet medical need and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

Data Exclusivity

Marketing authorization applications for generic medicinal products do not need to include the results of preclinical and clinical trials, but instead can refer to the data included in the marketing authorization of a reference product for which regulatory data exclusivity has expired. If a marketing authorization is granted for a medicinal product containing a new active substance, that product benefits from eight years of data exclusivity, during which generic MAAs referring to the data of that product may not be accepted by the regulatory authorities, and a further two years of market exclusivity, during which such generic products may not be placed on the market. The two-year period may be extended to three years if during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved.

Pediatric Development

In the European Union, companies developing a new medicinal product must agree to a Paediatric Investigation Plan, or PIP, with the EMA and must conduct pediatric clinical trials in accordance with that PIP, unless a deferral or waiver applies, (*e.g.*, because the relevant disease or condition occurs only in adults). The MAA for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Where the MAA includes the results of all pediatric studies conducted in accordance with the PIP and the results are reflected in the approved summary of product characteristics, the holder of a patent or supplementary protection certificate is entitled to receive a six month extension of the protection under a supplementary protection certificate or, in the case of orphan medicinal products, the product is eligible for a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Post-Approval Controls

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, or QPPV, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited.

Direct-to-consumer advertising of prescription medicines is also prohibited in the European Union. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each EU Member State and can differ from one country to another.

Pricing and Reimbursement in the European Union

Governments influence the price of medicinal products in the European Union through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies.

Other EU Member States allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union (commonly referred to as "Brexit"). Thereafter, on March 30, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Treaty on European Union. The withdrawal of the United Kingdom from the European Union was originally expected to take effect on March 29, 2019 but has since been extended. While a withdrawal agreement was agreed between the EU and the UK government, which included a transition period until the end of 2020, such agreement has been rejected by the UK Parliament on a number of occasions. At this time, we cannot anticipate what the timing and scope of Brexit will be. Additionally, Brexit has caused instability and uncertainty in the UK government and Parliament. The EMA is working under the assumption that the UK will become a third country as of the official date of departure from the EU, which as of the date of this filing is October 31, 2019. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, immediately following Brexit, it is expected that the United Kingdom's regulatory regime will remain aligned to European regulations. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom. In the longer term, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom.

Rest of World Regulation

For other countries outside of the United States and the European Union, such as China and Japan, the requirements governing clinical trials, marketing authorization, commercial sales and distribution of our products vary from jurisdiction to jurisdiction. Although many of the issues discussed above with respect to the United States and the European Union apply similarly in the context other geographies, the approval process varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Other Healthcare Laws and Regulations

In addition to FDA restrictions on the marketing of pharmaceutical products, other U.S. federal and state healthcare regulatory laws restrict business practices in the pharmaceutical industry. These laws include, but are not limited to the following:

- The federal Anti-Kickback Statute prohibits, among other things, any person or entity from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federally funded healthcare programs, such as Medicare and Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, formulary managers and beneficiaries on the other hand. The majority of states also have anti-kickback laws, which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers, or to self-pay patients;

- The federal civil and criminal false claims laws, including, without limitation, the federal civil monetary penalties law and the civil False Claims Act, prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment of federal funds and knowingly making, or causing to be made, a false record or statement material to a false or fraudulent claim to avoid, decrease or conceal an obligation to pay money to the federal government. Violations of the civil False Claims Act can result in very significant monetary penalties and treble damages. Many states also have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of payor;

- HIPAA, imposes criminal liability for executing or attempting to execute a scheme to defraud any healthcare benefit program and creates federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- The federal transparency requirements under the Physician Payments Sunshine Act require certain manufacturers of drugs, devices, biologics and medical supplies reimbursed under Medicare, Medicaid, or the Children's Health Insurance Program to report information related to payments and other transfers of value provided to physicians and teaching hospitals and physician ownership and investment interests. Failure to submit timely, accurately and completely the required information may result in civil monetary penalties;

- Data privacy and security regulation by both the federal government and the states in which we conduct business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts; and

- The FCPA prohibits any United States individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight and debarment from government contracts.

We will be required to spend substantial time and money to ensure that our business arrangements with third parties comply with applicable healthcare laws and regulations. Recent healthcare reform legislation has strengthened these federal and state healthcare laws. For example, the Affordable Care Act amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes to clarify that liability under these statutes does not require a person or entity to have actual knowledge of the statutes or a specific intent to violate them. Moreover, the Affordable Care Act provides that the government may assert that a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of these laws can subject us to criminal, civil and administrative sanctions including monetary penalties, damages, fines, disgorgement, individual imprisonment and exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and reputational harm, and we may be required to curtail or restructure our operations.

Coverage, Reimbursement and Pricing in the United States

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we obtain regulatory approval. The United States government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded drug and biologic products. In the United States and markets in other countries, patients who are prescribed products generally rely on third-party payors to reimburse all or part of the associated healthcare costs. If approved, sales of our product candidates will depend, in part, on the availability of coverage and adequate reimbursement from third-party payors. Third-party payors include government authorities, managed care plans, private health insurers and other organizations.

In the United States, the process for determining whether a third-party payor will provide coverage for a drug product typically is separate from the process for setting the price of such product or for establishing the reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication, or place products at certain formulary levels that result in lower reimbursement levels and higher cost-sharing obligation imposed on patients. A decision by a third-party payor not to cover our product candidates could reduce physician utilization of a product. Moreover, a third-party payor may not provide adequate third-party reimbursement to enable a manufacturer to maintain price levels sufficient to realize an appropriate return on its investment in product development. Additionally, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process usually requires manufacturers to provide scientific and clinical support for the use of their products to each payor separately and is a time-consuming process.

An increasing emphasis on cost containment measures in the United States will likely increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost-effectiveness of pharmaceutical products, in addition to questioning safety and efficacy. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover that product after FDA approval or, if they do, the level of payment may not be sufficient to allow a manufacturer to sell its product at a profit.

In addition, in many foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. The downward pressure on healthcare costs in general, particularly prescription products, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low-priced markets exert a commercial pressure on pricing within a country.

Health Care Reform

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and devices and to spur innovation, but its ultimate implementation is uncertain. In addition, in August 2017, the FDA Reauthorization Act was signed into law, which reauthorized the FDAs user fee programs and included additional drug and device provisions that build on the Cures Act.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products and services, implementing reductions in Medicare and other healthcare funding and applying new payment methodologies. For example, the Affordable Care Act, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs

coverage under Medicare Part D; subjected drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending. Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, and we expect there will be additional challenges and amendments to the Affordable Care Act in the future. In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act to reduce healthcare expenditures. These changes include the Budget Control Act of 2011, which, among other things, included aggregate reductions of Medicare payments to providers of 2% per fiscal year and that will remain in effect through 2025 unless additional action is taken by Congress; and the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for pharmaceutical and biologic products. Individual states in the United States have become increasingly active in passing legislation and implementing regulations designed to control biotechnology and pharmaceutical product pricing and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services.

The Separation and Distribution

In May 2018, Ironwood announced its plans to separate its sGC business from its commercial and gastrointestinal business. In furtherance of this plan, on March 6, 2019, Ironwood's board of directors approved the distribution of all of the issued and outstanding shares of our common stock on the basis of one share of our common stock for every 10 shares of Ironwood common stock issued and outstanding on March 19, 2019, the record date for the distribution.

On March 30, 2019 we also entered into a separation agreement with Ironwood, which is referred to in this prospectus as the separation agreement, and have since entered into various other agreements with Ironwood, including a tax matters agreement, an employee matters agreement, a development agreement, an intellectual property license agreement, a transition services agreement under which we temporarily receive certain services from Ironwood, and a second transition services agreement under which we temporarily provide certain services to Ironwood. These agreements also govern certain of our relationships with Ironwood after the separation. For additional information regarding the separation agreement and the other related agreements, see "Risk Factors—Risks Related to the Separation" and "Certain Relationships and Related Person Transactions—Agreements with Ironwood."

Competition

The biopharmaceutical industry is highly competitive within and across therapeutic categories and indications. There are many public and private biopharmaceutical companies, universities, government

agencies and other research organizations actively engaged in the research and development of products that may be similar to our product candidates or address similar markets. In addition, the number of companies seeking to develop and commercialize products and therapies competing with our product candidates is likely to increase. However, we seek to build our portfolio with key differentiating attributes to provide a competitive advantage in the markets we target. The success of all of our product candidates, if approved, is likely to be a result of their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

The sGC stimulator class of compounds has one major participant besides us. Bayer/Merck have an active collaboration on sGC modulators and may be targeting some of the same indications through a similar mechanism of action. They have one approved sGC stimulator, ADEMPAS® (riociguat), indicated for PAH and CTEPH, and an investigational sGC stimulator, vericiguat, in clinical development for heart failure. In addition, they have three sGC activator programs in early clinical development for chronic kidney disease, pulmonary hypertension, and acute respiratory distress syndrome.

Many of our competitors stated below may have greater financial resources and broader expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved medicines than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Olinciguat

In SCD, there are two approved products indicated to treat acute complications, such as painful crises, hydroxyurea (DROXIA® or SIKLOS®, as well as other generic forms) and ENDARI®, an amino acid l-glutamine. We are aware of the following companies engaged in the clinical development of products for the chronic treatment of SCD: Novartis, which is developing crizanlizumab (Phase 3), an IV-infusion anti-P-selectin monoclonal antibody, and ILARIS® (canakinumab) (Phase 2), a fully human monoclonal anti-human interleukin-1b antibody; Global Blood Therapeutics, Inc., which is developing voxelotor (Phase 3), a hemoglobin modulator; AstraZeneca plc, which is developing ticagrelor (Phase 3), a P2Y12 platelet inhibitor in pediatric and adolescent patients; Micelle BioPharma, Inc., which is developing SC411 (Phase 3), a mixture of fatty acids; Imara, Inc., which is developing IMR-687 (Phase 2), a phosphodiesterase-9 inhibitor, or PDE9i; and Pfizer Inc., which is developing PF-04447943 (Phase 1/2), a PDE9i. We are also aware of the following companies engaged in the clinical development of products for acute treatments in SCD: Pfizer Inc., which is developing rivipansel (Phase 3), a pan-selectin inhibitor; Prolong Pharmaceuticals, LLC which is developing Sanguinate (Phase 2), a PEGylated hemoglobin; and Modus Therapeutics AB, which is developing sevuparin (Phase 2), a cell adhesion molecule inhibitor. We may also face competition from one-time treatments such as HSCT, gene editing and gene therapy. We are aware of the following companies engaged in the clinical development of one-time treatments: bluebird bio, Inc. is currently conducting a Phase 1/2 study with their product, LentiGlobin®, for patients with severe SCD; and CRISPR Therapeutics AG/Vertex Pharmaceuticals, Inc. is conducting a Phase 1/2 study with their product, CTX-001; and Bioverativ/Sangamo is conducting a Phase 1/2 study with their product, BIVV-003. There are several other companies engaged in earlier stage clinical development for products targeting SCD.

Praliciguat

We are not aware of any therapies approved by the FDA or EMA for the treatment of HFpEF. We are aware of the following companies engaged in the clinical development of products for the treatment of HFpEF: Novartis is currently engaged in a Phase 3 program assessing ENTRESTO® a fixed-dose combination of sacubitril, a neprilysin inhibitor and valsartan, an angiotensin II receptor blocker, for the treatment of HFpEF. ENTRESTO is currently approved for HFrEF and it is possible that it is or will be used off-label in patients with HFpEF. Eli Lilly and Boehringer Ingelheim are currently conducting a Phase 3 program in HFpEF with JARDIANCE®, a sodium-glucose co-transporter-2 inhibitor or SGLT2 inhibitor. JARDIANCE is currently approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. AstraZeneca plc is currently conducting a Phase 3 program in HFpEF with FARXIGA®, a SGLT2 inhibitor. FARXIGA is currently approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. AstraZeneca plc is also conducting a Phase 2 trial in HFpEF with AZD4831, a myeloperoxidase modulator. Bayer/Merck are currently conducting a Phase 2 study with vericiguat, an sGC stimulator, assessing health-related quality of life in patients with HFpEF. Bayer/Merck have previously completed a smaller Phase 2 study with vericiguat in patients with HFpEF in which they observed improvement in disease-specific health status.

There are three approved products in the United States to treat DN, none of which have demonstrated a cessation of disease progression:

AVAPRO® (irbesartan), an angiotensin II receptor antagonist, indicated to reduce the rate of progression of nephropathy in patients with type 2 diabetes and hypertension. CAPOTEN® (captopril), angiotensin I converting enzyme inhibitor, indicated to reduce the rate of progression in patients with Type 1 insulin-dependent diabetes mellitus and retinopathy. COZAAR® (losartan), an angiotensin II receptor blocker, indicated to treat DN in patients with type 2 diabetes mellitus and a history of hypertension. We are aware of the following companies engaged in the late-stage clinical development of products for the treatment of DN:

AstraZeneca plc has a Phase 3 study ongoing with FARXIGA®, an SGLT2 inhibitor, assessing renal outcomes and cardiovascular mortality in patients with chronic kidney disease. Eli Lilly/Boehringer Ingelheim GmbH are currently conducting a Phase 3 program in DN with JARDIANCE. Janssen Pharmaceuticals has an ongoing Phase 3 program assessing INVOKANA®, a SGLT2 inhibitor, in patients with DN. In July 2018, Janssen Pharmaceuticals announced that they would be stopping the Phase 3 CREDENCE study early based on positive efficacy findings based on a recommendation from the study's Independent Data Monitoring Committee. INVOKANA is currently approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. An sNDA for INVOKANA was recently submitted for chronic kidney diseases in patients with type 2 diabetes. Bayer has a Phase 3 program ongoing for the investigational product finerenone, a mineralocorticoid receptor antagonist, assessing its effect in patients with DN. Bayer also has a Phase 2 program ongoing for BAY1142524, a chymase inhibitor, in patients with diabetic kidney disease. There are several other companies engaged in earlier stage clinical development for products targeting HFpEF and DN.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize medicines that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any medicines that we may develop. Our competitors also may obtain FDA or other regulatory approval for their medicines more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic medicines.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We depend on third-party CMOs for all of our requirements of raw materials, drug substance and drug product for our ongoing clinical trials of praliciguat, olinciguat and IW-6463 and our non-clinical research. We intend to continue to rely on CMOs for the supply of praliciguat, olinciguat and IW-6463 for all stages of clinical development and commercialization, as well as for the supply of any other product candidates that we may identify. We require all of our CMOs to conduct manufacturing activities in compliance with current GMP requirements.

We believe the manufacture of praliciguat, olinciguat and IW-6463 drug substance and drug product is from readily available raw materials and the processes are amenable to large-scale production and do not require unusual equipment or handling. We believe adequate supply of praliciguat, olinciguat and IW-6463 drug substance and drug product is readily available from our current CMOs to satisfy our immediate clinical and non-clinical demands. We obtain our supplies from these CMOs on a purchase order basis and do not have arrangements in place for long-term supply or redundant supply of praliciguat, olinciguat or IW-6463; however, we are working with our CMOs to implement improvements to our drug substance and drug product manufacturing processes to further ensure product capacity adequate to meet further development and commercial demands.

Facilities

We occupy approximately 114,000 rentable square feet of office and laboratory space in Cambridge, Massachusetts, comprising a portion of the facilities previously occupied by Ironwood. While a portion of such space is being altered for our use, we are subleasing another portion as temporary swing space from Ironwood. We have entered into a direct lease with BMR-Rogers Street LLC, or the Landlord, for our office and lab space which will expire in June 2029. We believe these facilities will be suitable and adequate for our needs for the near term.

Employees

As of April 1, 2019, we had approximately 143 employees, 58 of whom hold M.D. or Ph.D. degrees. Approximately 37 employees are in discovery research, 63 in our drug development organization, 11 in our strategy and corporate development organizations and 32 in general and administrative functions. None of our employees are subject to a collective bargaining agreement or represented by a trade or labor union. We consider our employee relations to be good.

Legal Proceedings

We are not a party to any material legal proceedings at this time. From time to time, we may be subject to various legal proceedings and claims, which may have a material adverse effect on our financial position or results of operations.

MANAGEMENT

Directors and Executive Officers

The following table sets forth the names and ages, as of April 1, 2019, and titles of executive officers and members of our board of directors. Certain biographical information with respect to those executive officers and directors follows the table.

Name	Age	Position
Peter M. Hecht, Ph.D.	55	Chief Executive Officer and Director
Mark G. Currie	64	President
William Huyett	63	Chief Financial Officer
Kevin Churchwell(2)	57	Director
George Conrades(1)	80	Director
Marsha Fanucci(3)	65	Director
Ole Isacson(2)	59	Director
Stephanie Lovell(1)	59	Director
Terrance McGuire(1)(3)	63	Director
Michael Mendelsohn(3)	64	Director
Amy Schulman(2)	58	Director

(1) member of our audit committee

(2) member of our compensation committee

(3) member of our nominating and corporate governance committee

Executive Officers

Peter M. Hecht, Ph.D. has served as our chief executive officer and a member of our board of directors since the completion of the separation. Dr. Hecht formerly served as Ironwood's chief executive officer and as a member of its board of directors from its founding in 1998 to March 2019. Under Dr. Hecht's leadership, Ironwood grew from nine Ph.D. scientists to a commercial biotechnology company. Prior to founding Ironwood, Dr. Hecht was a research fellow at Whitehead Institute for Biomedical Research. Dr. Hecht serves on the advisory board of Ariadne Labs. Dr. Hecht earned a B.S. in mathematics and an M.S. in biology from Stanford University, and holds a Ph.D. in molecular biology from the University of California at Berkeley. Dr. Hecht's experiences as the founder of a commercial biotechnology company and his tenure as its chief executive officer and a board member make him a valuable member of our board of directors.

Mark G. Currie has served as our President since the completion of the separation. Dr. Currie formerly served as Ironwood's senior vice president, chief scientific officer and president of research and development from 2002 to March 2019. Prior to joining Ironwood, Dr. Currie directed cardiovascular and CNS disease research as vice president of discovery research at Sepracor. Previously, Dr. Currie initiated, built and led discovery pharmacology and also served as director of arthritis and inflammation at Monsanto Company. Dr. Currie has served as a director of Ironwood since the completion of the separation. Dr. Currie earned a B.S. in biology from the University of South Alabama and holds a Ph.D. in cell biology from the Bowman-Gray School of Medicine of Wake Forest University.

William Huyett has served as our chief financial officer since the completion of the separation. Mr. Huyett previously served as Ironwood's chief operating officer from December 2017 to March 2019. Prior to Ironwood, Mr. Huyett spent 30 years with McKinsey and Company, Inc., in its Washington D.C., Zurich, and Boston offices. During his tenure at McKinsey, Mr. Huyett served clients

in the life sciences, industrial and other technology-intensive sectors. He has been a Senior Partner Emeritus at McKinsey since December 2015, and was previously a Senior Partner from July 1998 to December 2015. As a Senior Partner, Mr. Huyett was a leader in the firm's pharmaceutical and medical products and its strategy and corporate finance practices. He also served on McKinsey's Shareholder's Council (its board of directors), serving as chair of its Finance Committee. Prior to joining McKinsey, Mr. Huyett held a variety of line management positions in the automation industry with Allen-Bradley (now Rockwell Automation, Inc.). Mr. Huyett is non-executive Chair of the board of directors of the London Stock Exchange-listed Georgia Healthcare Group PLC and an independent Director of the LSE-listed Georgia Capital. He serves on several not-for-profit boards, including The Rockefeller University and the Marine Biological Laboratory in Woods Hole. He earned his B.S. in electronics engineering and his M.B.A. from the University of Virginia.

Non-management Directors

Kevin Churchwell has served as a member of our board of directors since the completion of the separation. Dr. Churchwell has been the President of Boston Children's Hospital since September 2018, and executive vice president of health affairs and chief operating officer at Boston Children's Hospital since August 2013. Before joining Boston Children's Hospital, Dr. Churchwell was the chief executive officer of Nemours/Alfred I. duPont Hospital for Children from November 2010 to July 2013. Prior to that, Dr. Churchwell was the chief executive officer and executive director for the Monroe Carrell Jr. Children's Hospital, part of the Vanderbilt University Medical Center, from July 2007 to October 2010. Since 1993, Dr. Churchwell has been a clinician and faculty member at Boston Children's Hospital and Vanderbilt University Medical Center and was recently appointed the Robert and Dana Smith Associate Professor of Anesthesia at Harvard Medical School. Dr. Churchwell graduated with a B.S. in Biology from the Massachusetts Institute of Technology and received his M.D. from Vanderbilt Medical School.

Dr. Churchwell's vast experience as a clinician, researcher, hospital executive and administrator provides important and valuable perspective to our board of directors in designing and implementing patient treatments.

George Conrades has served as a member of our board of directors since the completion of the separation. Mr. Conrades has served as an executive advisor to Akamai Technologies, Inc., or Akamai, since June 2018. Previously, Mr. Conrades was the chairman of Akamai from August 2010 until March 2018, and executive chairman from 2005 to 2010. Mr. Conrades was both chairman and chief executive officer of Akamai from 1999 to 2005. Mr. Conrades has been a managing partner at Longfellow Venture Partners since 2009, and was a venture partner of Polaris Venture Partners from 1998 to 2012, where he is now partner emeritus. From 1997 to 1998, Mr. Conrades served as executive vice president of GTE and president of GTE Internetworking. Mr. Conrades served as chief executive officer of BBN Corporation from 1994 until its acquisition by GTE Internetworking in 1997. Prior to joining BBN Corporation, Mr. Conrades was a senior vice president at International Business Machines Corporation, or IBM, and a member of IBM's corporate management board. Mr. Conrades has served as a director of Oracle Corporation since 2008 and was previously a director of Harley Davidson, Inc. from 2002 to April 2016, Akamai from 1998 to March 2018, and Ironwood from 2005 until April 2016. Additionally, Mr. Conrades currently serves as life trustee on the board of Ohio Wesleyan University. Mr. Conrades received a B.A. in physics and math from Ohio Wesleyan University and an M.B.A. from the University of Chicago.

Mr. Conrades' experience as chief executive officer of two public companies and as division president at two additional high technology companies, coupled with his past and present directorships and trusteeships, make him an important member of our board of directors, particularly with respect to our corporate governance, growth strategy and business plans.

Marsha Fanucci has served as a member of our board of directors since March 2019. Ms. Fanucci served as senior vice president and chief financial officer of Millennium Pharmaceuticals, Inc. from July 2004 through January 2009, where she was responsible for corporate strategy, treasury, financial planning and reporting and operations. While at Millennium, she also served as vice president, finance and corporate strategy and vice president, corporate development and strategy. Previously, she was vice president of corporate development and strategy at Genzyme Corporation, a biotechnology company, from 1998 to 2000. From 1987 to 1998, Ms. Fanucci was employed at Arthur D. Little, Inc. where she most recently served as vice president and director. Ms. Fanucci has served on the board of directors of Alnylam Pharmaceuticals, Inc. and Syros Pharmaceuticals, Inc. since 2010 and 2015, respectively. Previously, she served on the board of directors of Ironwood and Momenta Pharmaceuticals, Inc. She received her B.S. in pharmacy from West Virginia University and her M.B.A. from Northeastern University.

Because of her extensive financial experiences at Millennium Pharmaceuticals and Genzyme in addition to her current and former directorships at Ironwood, Syros Pharmaceuticals, Alnylam Pharmaceuticals and Momenta Pharmaceuticals, Ms. Fanucci provides valuable industry insight and essential financial expertise as we execute our corporate objectives.

Ole Isacson has served as a member of our board of directors since the completion of the separation. Dr. Isacson has been professor of neurology and neuroscience at Harvard Medical School since 2002. Prior to his current role, Dr. Isacson served in a number of academic roles at Harvard Medical School. Since its founding in 2005, Dr. Isacson has been principal faculty of the Harvard Stem Cell Institute and is the founding director of the Neuroregeneration Institute at McLean Hospital, where he has served as a director since 2010. From September 2016 to May 2017, Dr. Isacson was the chief scientific officer and senior vice president for Pfizer Inc.'s Neuroscience and Pain Worldwide R&D division. Dr. Isacson received his Medical Bachelor and Doctor of Medicine degrees from the University of Lund in Sweden.

Dr. Isacson brings significant medical and scientific insight to our board of directors, as well as experience leading the R&D function of a multinational biopharmaceutical company.

Stephanie Lovell has served as a member of our board of directors since the completion of the separation. Ms. Lovell has served as the executive vice president, Medicare and chief legal officer for Blue Cross Blue Shield of Massachusetts, Inc., or BCBSMA, since July 2015. Ms. Lovell previously served as the senior vice president and general counsel of BCBSMA from December 2011 to July 2015. Prior to BCBSMA, Ms. Lovell was the senior vice president of administration and general counsel for Boston Medical Center from March 2007 to December 2011. She also previously served as the first assistant attorney general in the Massachusetts Office of the Attorney General and as the executive director for the Massachusetts State Ethics Commission. Ms. Lovell currently serves as a director of the New England Law Foundation and The Partnership, Inc., and as a trustee of the Massachusetts Taxpayers Foundation. She also chairs the grants committee of the Boston Bar Foundation and is a member of the investment committee of Goodwill Industries of Massachusetts. Ms. Lovell received a B.A. in philosophy from Hamilton College and a J.D. from Boston University School of Law.

Ms. Lovell brings to our board of directors invaluable experience in the healthcare payer and reimbursement markets, as well as government and regulatory affairs, providing important perspective and insight to our board of directors.

Terrance McGuire has served as a member of our board of directors since the completion of the separation. Mr. McGuire was a co-founder and is currently a general partner of Polaris Partners. Prior to founding Polaris Partners in 1996, Mr. McGuire spent seven years at Burr, Egan, Deleage & Co., investing in early stage medical and information technology companies. Mr. McGuire currently serves on the board of directors of Arsanis, Inc. and Pulmatrix, Inc. and several private companies. Previously, he served on the boards of Ironwood, Acceleron Pharma, Inc., Akamai Technologies, Inc., Aspect

Medical Systems, Inc., Cubist Pharmaceuticals, Inc., deCODE genetics, Inc., Trevena, Inc. and various private companies. Mr. McGuire is the former chairman of the National Venture Capital Association, which represents 90% of the venture capitalists in the U.S., chairman of the board of the Thayer School of Engineering at Dartmouth College, and a member of the boards of The David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology and The Arthur Rock Center for Entrepreneurship at Harvard Business School. Mr. McGuire earned a B.S. in physics and economics from Hobart College, an M.S. in engineering from The Thayer School at Dartmouth College, and an M.B.A from Harvard Business School.

Mr. McGuire brings to our board extensive experience as a venture capitalist focused on the biotechnology industry, as well as many years of experience as a director of biotechnology companies guiding them in the execution of their corporate strategy and objectives.

Michael Mendelsohn has served as a member of our board of directors since the completion of the separation. Dr. Mendelsohn has been the executive chairman and president of Cardurion Pharmaceuticals since May 2016 and is the president of the Mendelsohn Consulting Group LLC, which he formed in September 2013. Since April 2015, Dr. Mendelsohn has been a senior advisor and consultant to the chief medical and scientific officer of Takeda Pharmaceutical Co. Ltd. and, since December, 2014, has served as senior advisor and consultant and a member of the pharmaceuticals advisor committee for the chief scientific officer and president of R&D at Ironwood. From May 2014 until July 2017, Dr. Mendelsohn was a venture partner for SV Health Investors. Prior to that, Dr. Mendelsohn was the senior vice president and global head of cardiovascular research at Merck Research Laboratories from June 2010 to November 2013. From 1993 to 2010, Dr. Mendelsohn served in various roles at Tufts Medical Center and Tufts University School of Medicine, including as founder and executive director of the Molecular Cardiology Research Institute and as chief scientific officer from 2008 to 2010. Previously, Dr. Mendelsohn was a member of the cardiovascular faculty at Brigham and Women's Hospital and Harvard Medical School. Dr. Mendelsohn serves as a director of Foghorn Therapeutics, Inc. and previously served on the board of directors of Regado Biosciences Inc. from November 2013 to May 2015. Dr. Mendelsohn received a B.A. in chemistry and English from Amherst College and a M.D. from Harvard Medical School.

Dr. Mendelsohn brings extensive experience to our board of directors as a clinician and scientist, along with his insights as a consultant to lead researchers for multinational biopharmaceutical companies.

Amy Schulman has served as a member of our board of directors since the completion of the separation. In July 2015, Ms. Schulman co-founded and joined Lyndra, Inc. as chief executive officer. In February 2017, she became chief executive officer of Olivo Laboratories, LLC. Ms. Schulman is also a senior lecturer at Harvard Business School, where she was appointed to the faculty in July 2014, and has been a partner at Polaris Partners since August 2014. Ms. Schulman served as chief executive officer of Arsia Therapeutics, Inc. from August 2014 to November 2016 when Arsia was acquired by Eagle Pharmaceuticals, Inc. Ms. Schulman was previously the executive vice president and general counsel of Pfizer Inc. from May 2008 to July 2014, where she also served as the business unit lead for Pfizer's consumer healthcare business from April 2012 to December 2013. Before joining Pfizer, she was a partner at the law firm DLA Piper, where she was a member of the board and executive policy committees. Ms. Schulman has also served as a director of Arsanis, Inc. and Alnylam Pharmaceuticals, Inc. since 2015 and 2014, respectively. Previously, she served as a director of Ironwood, BIND Therapeutics, Inc. and Blue Buffalo Pet Products, Inc. Ms. Schulman graduated with honors with B.A. degrees in philosophy and English from Wesleyan University, where she was elected to Phi Beta Kappa, and earned her J.D. from Yale Law School in 1989.

Ms. Schulman brings to our board of directors extensive leadership experience in the biotechnology industry in areas of great importance to the success of our business as we execute on our corporate objectives, including commercial strategy, corporate development and capability building.

Board Composition and Independence

Our business and affairs are managed under the direction of our board of directors. Our board of directors consists of nine members. Our directors hold office until their successors have been elected and qualified or until their earlier death, resignation or removal. Our board of directors has determined that Messrs. Churchwell, Conrades, Isacson, McGuire and Mendelsohn, and Mses. Fanucci, Lovell and Shulman satisfy the independence standard established by the listing standards of the Nasdaq Global Select Market, or Nasdaq, as well as the corporate governance principles adopted by our board of directors. There are no family relationships among any of our directors or executive officers.

Board Committees

Our board of directors has three standing committees: an audit committee, a compensation committee and a nominating and corporate governance committee, each of which operates pursuant to a charter adopted by our board of directors.

Audit Committee

Our audit committee provides oversight of our accounting and financial reporting process, the audit of our financial statements and our internal controls function. Among other matters, the audit committee is responsible for the following:

- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements, earnings releases and related disclosures;
- reviewing and discussing with management and our independent registered public accounting firm our internal controls and internal auditing procedures, including any material weaknesses in either;
- discussing our accounting policies and all material correcting adjustments with our management and our independent registered public accounting firm;
- discussing with our management and our independent registered public accounting firm any significant risks facing the company and the related mitigation plans, as well as monitoring our internal control over financial reporting and disclosure controls and procedures;
- appointing, overseeing and approving the compensation for and, when necessary, terminating our independent registered public accounting firm;
- approving all audit services and all permitted non-audit, tax and other services to be performed by our independent registered public accounting firm, in each case, in accordance with the audit committee's pre-approval policy;
- discussing with the independent registered public accounting firm its independence and ensuring that it receives the written disclosures regarding these communications required by the Public Company Accounting Oversight Board;
- reviewing and approving all related party transactions;
- recommending whether the audited financial statements should be included in our annual report and preparing the audit committee report required by SEC rules;

- reviewing all material communications between our management and our independent registered public accounting firm;
- reviewing, updating and recommending to our board changes to our code of business conduct and ethics; and
- establishing procedures for the receipt, retention, investigation and treatment of accounting related complaints and concerns.

The members of our audit committee are Ms. Lovell, Mr. McGuire and Mr. Conrades, who serves as chair, each of whom meets the independence requirements of applicable Nasdaq and SEC rules. Each member of the audit committee is financially literate and has accounting or related financial management expertise. Additionally, our board of directors has determined that Mr. Conrades is an "audit committee financial expert" under applicable Nasdaq and SEC rules.

Compensation Committee

Our compensation committee intends to adopt, and will administer, compensation policies, plans and benefit programs for our executive officers and all other members of our executive team. Our compensation committee is also responsible for:

- reviewing and approving corporate goals and objectives relevant to executive officer compensation and evaluating the performance of executive officers in light of those goals and objectives;
- reviewing and approving executive officer compensation, including salary, bonus and incentive compensation, deferred compensation, perquisites, equity compensation, benefits provided upon retirement, severance or other termination of employment and any other forms of executive compensation;
- reviewing and approving our chief executive officer's compensation based on its evaluation of our chief executive officer's performance;
- overseeing and administering our incentive compensation plans and equity based plans and recommending the adoption of new incentive compensation plans and equity based plans to our board of directors;
- making recommendations to our board of directors with respect to director compensation; and
- making recommendations to our board of directors with respect to management succession planning, including planning with respect to our chief executive officer.

The compensation committee is comprised of Dr. Churchwell, Dr. Isacson and Ms. Schulman, who serves as chair, each of whom meets the independence requirements of applicable Nasdaq and SEC rules, and each of whom qualifies as a "non-employee director" (within the meaning of Rule 16b-3 of the Exchange Act) and an "outside director" (within the meaning of Section 162(m) of the Code).

Nominating and Corporate Governance Committee

Our nominating and corporate governance committee is responsible for, among other duties:

- identifying individuals qualified to become members of our board of directors;
- recommending to our board of directors the persons to be nominated for election as directors;
- assisting our board of directors in recruiting such nominees;
- recommending to our board of directors qualified individuals to serve as committee members;

- performing an annual evaluation of our board of directors;
- evaluating the need and, if necessary, creating a plan for the continuing education of our directors;
- assessing and reviewing our corporate governance guidelines and recommending any changes to our board of directors; and
- evaluating and approving any requests from our executives to serve on the board of directors of another for-profit company.

The nominating and corporate governance committee is comprised Ms. Fanucci, Dr. Mendelsohn and Mr. McGuire, who serves as chair, each of whom meets the independence requirements of Nasdaq.

Compensation Committee Interlocks and Insider Participation

There were no relationships during the fiscal year ended December 31, 2018 which qualify as a compensation committee interlock under applicable SEC rules.

Corporate Governance Principles and Code of Conduct

Our board of directors has adopted corporate governance principles that set forth the responsibilities of the board of directors and the qualifications and independence of its members and the members of its standing committees. In addition, our board of directors adopted a code of conduct setting forth standards applicable to all of our directors, officers and employees. The corporate governance principles and code of conduct are available on our website at *www.cyclerion.com*. We expect that any amendment to the code, or any waivers of its requirements, that apply to our chief executive officer, chief financial officer, chief accounting officer, or corporate controller, if any, will be disclosed on our website.

EXECUTIVE COMPENSATION

Executive Compensation

Overview

Prior to April 1, 2019, we were managed and operated in the normal course of business under Ironwood. Accordingly, during the fiscal year 2018 we did not pay any compensation to any of our executive officers or employees. However, our operations under Ironwood are being carried on by us following the separation and the executives who managed our business under Ironwood are our executive officers after the separation.

The following tables and discussion relate to the compensation paid to Peter M. Hecht, Ph.D., who currently serves as our Chief Executive Officer and, prior to the separation, served as the Chief Executive Officer of Ironwood, and the two most highly compensated executive officers (other than Dr. Hecht) who were serving as executive officers of Ironwood on the last day of fiscal year 2018. They are Mark G. Currie, Ph.D., who currently serves as our President and, prior to the separation, served as Senior Vice President, Chief Scientific Officer and President of R&D of Ironwood, and William Huyett who currently serves as our Chief Financial Officer and, prior to the separation, served as Chief Operating Officer of Ironwood. Dr. Hecht, Dr. Currie and Mr. Huyett are referred to collectively in this prospectus as our "named executive officers."

Prior to the separation, the compensation of our named executive officers for their service to Ironwood was designed and determined by Ironwood and the Ironwood Compensation and HR Committee. In connection with the separation, our compensation committee adopted a similar compensation philosophy as that designed and determined by Ironwood and the Ironwood Compensation and HR Committee. We have also determined the terms of our equity incentive plan, director compensation plan and executive severance agreements, each of which is described in this prospectus.

Summary Compensation Table

The following table sets forth information about certain compensation awarded to, earned by or paid to our named executive officers under Ironwood's compensation and benefit plans and programs during fiscal years 2018 and 2017. In connection with the separation, our compensation committee is considering, and expects to adopt, our corporate compensation philosophy and the terms of our directors compensation plan. We have determined the terms of our equity incentive plan and executive severance agreements, each of which is described in this prospectus.

Name and Principal Position	Year	Salary ($)	Bonus ($)	Stock Awards ($)	Option Awards ($)	Nonequity Incentive Plan Compensation ($)	All Other Compensation ($)	Total ($)
Peter M. Hecht, Ph.D., *Chief Executive Officer*	2018(1)	100,000	1,192,500(2)	—	3,842,268(3)	—	25,348(4)	5,160,116
Mark G. Currie, Ph.D.,	2018	485,000	—	231,360	1,424,289(3)	242,500(5)	62,271(4)	2,445,420
President	2017	470,000	—	—	1,936,650(6)	210,000(7)	8,040(8)	2,624,690
William Huyett,	2018	465,000	—	1,090,298	2,346,469(3)	232,500(5)	8,040(4)	4,142,307
Chief Financial Officer	2017(9)	19,674	50,000(10)	—	—	—	6,078	75,752

(1) Dr. Hecht was not a named executive officer prior to 2019, therefore this table does not provide 2017 data for him.

(2) Consists of a one-time discretionary bonus approved by the Ironwood Compensation and HR Committee in fiscal year 2019 for fiscal year 2018 performance.

(3) Reflects the fair value of time-based restricted stock unit and stock option awards on the date of grant calculated in accordance with Financial Accounting Standards Board issued Accounting Standards Codification Topic 718, *Compensation—Stock Compensation*, or ASC 718. For a discussion of the policies used to determine assumptions used in

the valuation of awards, see Note 14 to Ironwood's consolidated financial statements for the year ended December 31, 2018 included in Ironwood's Annual Report on Form 10-K that Ironwood filed with the SEC on February 25, 2019. All values reported exclude the effects of potential forfeitures.

(4) Drs. Hecht and Currie received one-time payments of $17,308 and $54,231, respectively, for accrued but unused sabbatical leave balances that were paid in 2018 upon the termination of Ironwood's company-wide sabbatical program. Additionally, for each named executive officer, $6,000 of such amount consists of matching contributions made under the Ironwood 401(k) plan, as well as an amount attributable to a transportation stipend and a fitness stipend.

(5) Consists of payments made under Ironwood's annual cash bonus program in fiscal year 2019 for fiscal year 2018 performance.

(6) Reflects the fair value of stock option awards on the date of grant calculated in accordance with Financial Accounting Standards Board issued Accounting Standards Codification 718, *Compensation—Stock Compensation*, or ASC 718. For a discussion of the assumptions used in the valuation of awards, see Note 15 to Ironwood's consolidated financial statements for the year ended December 31, 2017 included in Ironwood's Annual Report on Form 10-K that Ironwood filed with the SEC on February 22, 2018. All values reported exclude the effects of potential forfeitures.

(7) Consists of payments made under Ironwood's annual cash bonus program in fiscal year 2018 for fiscal year 2017 performance.

(8) For each named executive officer, $6,000 of such amount consists of matching contributions made under the Ironwood 401(k) plan, as well as an amount attributable to a transportation stipend and a fitness stipend.

(9) Mr. Huyett was hired as Chief Operating Officer of Ironwood, effective December 15, 2017. Amounts shown in this row reflect Mr. Huyett's compensation from December 15, 2017 through December 31, 2017.

(10) Reflects a one-time bonus paid in connection with Mr. Huyett's hiring as Chief Operating Officer of Ironwood.

Chief Executive Officer Compensation

2018

Since 1998, when Dr. Hecht began serving as Ironwood's Chief Executive Officer, he has been paid an annual base salary of $100,000 and has declined increases to his base salary each year. Dr. Hecht's compensation was reviewed and approved annually by the Ironwood Compensation and HR Committee. In January 2018, the Ironwood Compensation and HR Committee recommended an increase to Dr. Hecht's base salary to be market competitive with his peers, but Dr. Hecht declined to accept such increase.

In January 2018, Ironwood's Compensation and HR Committee recommended, and Dr. Hecht declined to accept, a cash bonus for Dr. Hecht based on Ironwood's achievement of 84% of its fiscal year 2017 corporate goals. Since co-founding Ironwood in 1998, Dr. Hecht has declined cash bonuses each year. Recognizing that Dr. Hecht's cash compensation is well below his market peers, the Ironwood Compensation and HR Committee granted Dr. Hecht stock options, in lieu of an increase to base salary and cash bonus, to keep his overall compensation competitive with that of his peers.

The Ironwood Compensation and HR Committee set the fiscal year 2018 equity pool based on Ironwood's achievement of its fiscal year 2017 corporate goals at 84% and then set individual award amounts based on peer group and market data, with adjustments for relative company performance and individual performance. Each of Ironwood's executive officers, including Dr. Hecht, was given the opportunity to choose from among the following mix for his or her fiscal year 2018 annual equity awards: 100% stock options, 75% stock options and 25% restricted stock units, or 50% stock options and 50% restricted stock units.

On February 21, 2018, Dr. Hecht was granted an annual equity award of 390,000 options to purchase shares of Ironwood common stock and 190,000 options to purchase shares of Ironwood common stock in lieu of a cash bonus or base salary increase. The stock options have an exercise price equal to the fair market value of a share of Ironwood common stock on the grant date and vest over four years as to 1/48th of the award on each monthly anniversary of the vesting commencement date, which was January 1, 2018.

2019

In January 2019, the Ironwood Compensation and HR Committee recommended an increase to Dr. Hecht's base salary to be market competitive with his peers, but Dr. Hecht declined to accept such increase.

The Ironwood Compensation and HR Committee set the fiscal year 2019 equity pool based on Ironwood's achievement of its fiscal year 2018 corporate goals at 100% and the price of Ironwood's common stock and set individual award amounts based on peer group and market data, with adjustments for relative company performance and individual performance. Each of Ironwood's executive officers, including Dr. Hecht, was given the opportunity to choose from among the following mix for his or her fiscal year 2019 annual equity awards: 100% stock options, 75% stock options and 25% restricted stock units, or 50% stock options and 50% restricted stock units.

In recognition of Ironwood's achievement of 100% of its fiscal year 2018 corporate goals as well as recognizing that Dr. Hecht's cash compensation is well below his market peers, Ironwood's Compensation and HR Committee recommended an annual equity award of 1,000,000 options to purchase shares of Ironwood common stock and a cash bonus of $1,192,500 in January 2019. While the Ironwood Compensation and HR Committee has historically granted Dr. Hecht stock options in lieu of an increase to base salary and cash bonus, and to keep his overall compensation competitive with that of his peers, Dr. Hecht accepted a portion of his fiscal year 2018 bonus in the form of cash, rather than stock options, due to limitations on annual equity grants to individuals under Ironwood's equity incentive plans.

Dr. Hecht's stock options were awarded on January 29, 2019 and have an exercise price equal to the fair market value of a share of Ironwood common stock on the grant date and vest over four years as to 1/48th of the award on each monthly anniversary of the vesting commencement date, which was January 1, 2019.

Other Named Executive Officer Compensation

Base Salaries

At Ironwood, base salaries served to provide a stable source of income. They are determined at commencement of employment and generally re-evaluated annually and adjusted, if warranted, to realign salaries with market levels and to reflect the performance of the executive officer.

In January 2018, the Ironwood Compensation and HR Committee reviewed and approved a $15,000 increase in Dr. Currie's base salary from $470,000 to $485,000 in recognition of his meeting or exceeding all or substantially all of his individual performance goals in 2017. The Ironwood Compensation and HR Committee also took into account peer group and other market data provided by Pearl Meyer & Partners, LLC or PM, its compensation consultant. In December 2017, the Ironwood Compensation and HR Committee approved an initial base salary for Mr. Huyett of $465,000, based on peer group and other market data provided by PM. Mr. Huyett did not receive an increase in base salary, due to the short period of time between his joining Ironwood on December 15, 2017 and the Ironwood Compensation and HR Committee's 2018 base salary reviews.

In January 2019, the Ironwood Compensation and HR Committee reviewed and approved a $15,000 increase in Dr. Currie's base salary from $485,000 to $500,000 and a $20,000 increase in Mr. Huyett's salary from $465,000 to $485,000 in recognition of each of Dr. Currie's and Mr. Huyett's meeting or exceeding all or substantially all of his individual performance goals in 2018. The Ironwood Compensation and HR Committee also took into account peer group and other market data provided by PM.

Bonuses

Dr. Currie received payments in 2018 under Ironwood's annual cash bonus program based on fiscal year 2017 performance. For fiscal year 2017, Dr. Currie had an individual bonus target at Ironwood of 50% of base salary. In January 2018, following the recommendations of Dr. Hecht, the Ironwood Compensation and HR Committee reviewed and approved a bonus of $210,000 for Dr. Currie for fiscal year 2017 performance. 70% percent of Dr. Currie's fiscal year 2017 bonus amount was tied solely to Ironwood's achievement of 84% percent of its corporate goals, and 30% was tied to both Ironwood's achievement of corporate goals and Dr. Currie's achievement of his individual goals. Dr. Currie met or exceeded all or substantially all of his individual goals for fiscal year 2017.

Mr. Huyett was not eligible for a bonus in respect of fiscal year 2017 due to the substantial completion of fiscal year 2017 when he joined Ironwood. However, Mr. Huyett did receive a one-time cash bonus of $50,000 in connection with his hiring in December 2017.

Each of Dr. Currie and Mr. Huyett received payments in 2019 under Ironwood's annual cash bonus program based on fiscal year 2018 performance. For fiscal year 2018, each of Dr. Currie and Mr. Huyett had an individual bonus target at Ironwood of 50% of base salary. In January 2019, following the recommendations of Dr. Hecht, the Ironwood Compensation and HR Committee reviewed and approved a bonus of $242,500 for Dr. Currie and $232,500 for Mr. Huyett for fiscal year 2018 performance. 70% percent of each of Dr. Currie's and Mr. Huyett's fiscal year 2018 bonus amount was tied solely to Ironwood's achievement of 100% percent of its corporate goals, and 30% was tied to both Ironwood's achievement of corporate goals and the executive's achievement of his individual goals. Each of Dr. Currie and Mr. Huyett met or exceeded all or substantially all of his individual goals for fiscal year 2018.

Equity-Based Compensation

2018

Drs. Hecht and Currie were each granted an Ironwood annual equity award in fiscal year 2018. The Ironwood Compensation and HR Committee set the fiscal year 2018 equity pool based on Ironwood's achievement of its fiscal year 2017 corporate goals at 84% and then set individual award amounts based on peer group and market data, with adjustments for relative company performance and individual performance.

Each of Ironwood's executive officers, including Drs. Hecht and Currie, was given the opportunity to choose from among the following mix for his or her fiscal year 2018 annual equity awards: 100% stock options, 75% stock options and 25% restricted stock units, or 50% stock options and 50% restricted stock units.

On February 21, 2018, Dr. Currie was granted an annual equity award of 215,000 options to purchase shares of Ironwood common stock. The stock options have an exercise price equal to the fair market value of a share of Ironwood common stock on the grant date and vest over four years as to 1/48th of the award on each monthly anniversary of the vesting commencement date, which was January 1, 2018. In addition, on July 31, 2018, Dr. Currie was granted 12,000 restricted stock units for shares of Ironwood common stock in recognition of his service to Ironwood in connection with the separation. The restricted stock units will vest in full on May 9, 2019.

Mr. Huyett was not eligible to receive an Ironwood annual equity award for fiscal year 2018 due to the substantial completion of fiscal year 2017 when he joined Ironwood and instead received an initial grant in early fiscal year 2018. On January 2, 2018, Mr. Huyett received an initial grant of 337,500 options and 56,250 restricted stock units, each for shares of Ironwood common stock. The stock options have an exercise price equal to the fair market value of a share of Ironwood common stock on the grant date. The stock options will vest over four years as to 25% of the shares on the first anniversary

of Mr. Huyett's start date and as to 1/48th of the total shares each month thereafter for the next 36 months, and the restricted stock units will vest as to 25% of the award on each anniversary of the grant date. In addition, on July 31, 2018, Mr. Huyett was granted 12,000 restricted stock units for shares of Ironwood common stock in recognition of his service to Ironwood in connection with the separation. The restricted stock units will vest in full on May 9, 2019.

2019

Each of our named executive officers was granted an Ironwood annual equity award in fiscal year 2019. The Ironwood Compensation and HR Committee set the fiscal year 2019 equity pool based on Ironwood's achievement of its fiscal year 2018 corporate goals at 100% and the price of Ironwood's common stock and then set individual award amounts based on peer group and market data, with adjustments for relative company performance and individual performance.

Each of Ironwood's executive officers, including the named executive officers, was given the opportunity to choose from among the following mix for his or her fiscal year 2019 annual equity awards: 100% stock options, 75% stock options and 25% restricted stock units, or 50% stock options and 50% restricted stock units.

On January 29, 2019, Dr. Currie was granted an annual equity award of 600,000 options to purchase shares of Ironwood common stock. The stock options have an exercise price equal to the fair market value of a share of Ironwood common stock on the grant date and vest over four years as to 1/48th of the award on each monthly anniversary of the vesting commencement date, which was January 1, 2019.

On January 29, 2019, Mr. Huyett was granted an annual equity award of 258,750 options to purchase shares of Ironwood common stock and 43,125 restricted stock units for shares of Ironwood common stock. The stock options have an exercise price equal to the fair market value of a share of Ironwood common stock on the grant date and vest over four years as to 1/48th of the award on each monthly anniversary of the vesting commencement date, which was January 1, 2019. The restricted stock units vest over four years as to 25% of the award on each anniversary of the vesting commencement date.

Employee Benefits

At Ironwood, our named executive officers were eligible to participate in Ironwood's broad-based health, welfare and fringe benefit plans. These plans include medical, dental, vision, basic and supplemental life, short-term and long-term disability insurance, flexible spending accounts, an employee assistance program, commuter benefits, a relocation program and transportation and fitness stipends. Our named executive officers were eligible to participate in these plans on the same basis as Ironwood's other eligible employees.

In connection with Ironwood's termination of its company-wide sabbatical program, employees, including Drs. Hecht and Currie, were paid out any accrued but unused sabbatical leave balances in fiscal year 2018.

In fiscal year 2018, our named executive officers participated in Ironwood's broad-based 401(k) plan, which provides a 75% matching company contribution on the first $8,000 of an employee's annual contribution to the 401(k) plan. Ironwood does not sponsor or maintain any qualified or non-qualified defined benefit plans or supplemental executive retirement plans.

Other than Ironwood's broad-based benefits, or as otherwise described herein, none of our named executive officers received perquisites of any nature in fiscal year 2018.

Agreements with our Named Executive Officers

On April 1, 2019, the Company entered into offer letters with each of Dr. Hecht, Dr. Currie, and Mr. Huyett. Pursuant to these offer letters, Dr. Hecht will receive an initial base salary of $100,000 per year, Dr. Currie will receive an initial base salary of $500,000 per year, and Mr. Huyett will receive an initial base salary of $485,000 per year. Each executive will have an individual bonus target of 50% of his base salary, subject to achievement of corporate goals.

Each of Dr. Hecht, Dr. Currie and Mr. Huyett have entered into a severance agreement with us that entitles him to receive certain benefits in the event of an involuntary termination without "cause" or a "constructive termination," including in the event of a "change of control termination" (each as defined in the agreement). Our severance agreements with each of Dr. Hecht, Dr. Currie and Mr. Huyett apply to any termination without cause, constructive termination or change of control termination occurring within six months following the effective date of such severance agreement.

Severance Benefits not in Connection with a Change of Control

Dr. Hecht. In the event of a termination without cause or a constructive termination not qualifying as a change of control termination, Dr. Hecht is entitled to receive (i) an amount equal to 18 months of his base salary for the year of termination; (ii) a pro rata amount of his target cash bonus for the year of termination (pro-rated based on the percentage of the year worked prior to the triggering event); (iii) an amount equal to his actual bonus for the prior year if not yet paid; (iv) an additional amount equal to his full target cash bonus for the year of termination, multiplied by 1.5; (v) 18 months of subsidized COBRA benefits; and (vi) outplacement benefits.

In addition, Dr. Hecht's severance agreement provides that any outstanding equity awards subject solely to time-based vesting vest in (1) the portion of the equity award that would have vested had he remained employed for 24 months following the termination date and (2) an additional portion of the equity award that would have vested on the next regular vesting date after such 24-month period as if the equity award vested on a daily basis from the last regular award vesting date occurring prior to the end of the 24-month period through such next regular vesting date. Any equity awards that did not vest pursuant to the preceding sentence will remain outstanding and eligible to vest upon the occurrence of a change of control termination (as defined below). Further, the exercisability of any outstanding vested stock options held by Dr. Hecht as of the termination date (including any vested options to purchase our common stock granted in connection with the separation) will be extended for 36 months following the termination date (or, in the event that we publicly announced that we are conducting negotiations leading to a change of control or entered into a definitive agreement that will result in a change of control during such 36-month period, the later of (i) the expiration of the 36-month period or (ii) the first to occur of the date that is three months following the change of control and 30 days following the date on which we announced that such definitive agreement had been terminated or that our efforts to consummate the change of control contemplated by the previously announced negotiations or by a previously executed definitive agreement had been abandoned).

Dr. Currie and Mr. Huyett. In the event of a termination without cause or a constructive termination not qualifying as a change of control termination, each of Dr. Currie and Mr. Huyett are entitled under their severance agreements to receive (i) an amount equal to 12 months of his base salary for the year of termination, plus an amount equal to a maximum of six months of his base salary for any period beginning as of the first anniversary during which he has not secured new, reasonably similar full-time employment; (ii) a pro rata amount of his target cash bonus for the year of termination (pro rated based on the percentage of the year worked prior to the triggering event); (iii) an amount equal to his actual bonus for the prior year if not yet paid; (iv) an additional amount equal to his full target cash bonus for the year of termination; (v) 12 months of subsidized COBRA benefits, plus up to an additional six months of subsidized COBRA benefits for any period beginning as

of the first anniversary during which he is not eligible to participate in the group medical plan of another employer; and (vi) outplacement benefits.

In addition, each of Dr. Currie's and Mr. Huyett's severance agreements provide that any outstanding equity awards subject solely to time-based vesting will vest in (1) the portion of the equity award that would have vested if the named executive officer had remained employed for 18 months following the termination date and (2) an additional portion of the equity award that would have vested on the next regular vesting date after such 18-month period as if the equity award vested on a daily basis from the last regular award vesting date occurring prior to the end of the 18-month period through such next regular vesting date. Any equity awards that did not vest pursuant to the preceding sentence will remain outstanding and eligible to vest upon the occurrence of a change of control termination (as defined below). Further, the exercisability of any outstanding vested stock options held by the named executive officer as of the termination date (including any vested options to purchase our common stock granted in connection with the separation) will be extended for 24 months following the termination date (or, in the event that we publicly announced that we are conducting negotiations leading to a change of control or entered into a definitive agreement that will result in a change of control during such 24-month period, the later of (i) the expiration of the 24-month period or (ii) the first to occur of the date that is three months following the change of control and 30 days following the date on which we announced that such definitive agreement had been terminated or that our efforts to consummate the change of control contemplated by the previously announced negotiations or by a previously executed definitive agreement had been abandoned).

Change of Control Severance Benefits

Dr. Hecht. In the event of a change of control termination, in lieu of any benefits under our broad-based change of control plan, Dr. Hecht is entitled to receive the following benefits under his severance agreement: (i) a lump-sum payment in an amount equal to 24 months of base salary as of the time of termination; (ii) a pro rata amount of his target cash bonus for the year of termination (pro-rated based on the percentage of the year worked prior to the triggering event); (iii) an amount equal to his actual bonus for the prior year if not yet paid; (iv) an additional amount equal to his full target cash bonus for the year of termination, multiplied by 2.0; (v) 24 months of subsidized COBRA benefits; and (vi) outplacement benefits.

In addition, in the event of a change of control termination, Dr. Hecht's severance agreement provides for acceleration of all outstanding equity awards subject solely to time-based vesting as of the later of (1) the termination date or (2) the change of control. Further, the exercisability of any outstanding vested stock options held by Dr. Hecht as of the termination date (including any vested options to purchase our common stock granted in connection with the separation) will be extended for 36 months following the termination date (or, if later the date that was three months following the change of control).

Dr. Currie and Mr. Huyett. In the event of a change of control termination, in lieu of any benefits under Ironwood's broad-based change of control plan, each of Dr. Currie and Mr. Huyett are entitled to receive the following benefits under their Ironwood severance agreements: (i) a lump-sum payment in an amount equal to 18 months of base salary as of the time of termination; (ii) a pro rata amount of his target cash bonus for the year of termination (pro-rated based on the percentage of the year worked prior to the triggering event); (iii) an amount equal to his actual bonus for the prior year if not yet paid; (iv) an additional amount equal to his full target cash bonus for the year of termination, multiplied by 1.5; (v) 18 months of subsidized COBRA benefits; and (vi) outplacement benefits.

In addition, in the event of a change of control termination, each of Dr. Currie's and Mr. Huyett's severance agreements provide for acceleration of all outstanding equity awards subject solely to time-based vesting as of the later of (1) the termination date or (2) the change of control. Further, the

exercisability of any outstanding vested stock options held by the named executive officer as of the termination date (including any vested options to purchase our common stock granted in connection with the separation) will be extended for 24 months following the termination date (or, if later the date that was three months following the change of control).

Under each of Drs. Hecht's and Currie's and Mr. Huyett's severance agreements, a change of control termination consists of an involuntary termination without "cause" or a "constructive termination" (each as defined in the agreement), in either event during the period commencing six months prior to the earlier of (1) the date that we first publicly announce that we are conducting negotiations leading to a change of control, or (2) the date that we enter into a definitive agreement that would result in a change of control, and ending on the earlier of (i) the date on which we announce that the definitive agreement has been terminated or the negotiations have been abandoned or (ii) the date that is 24 months after the change of control. Under each severance agreement, a change of control occurs when: (i) any person becomes, pursuant to a transaction or a series of transactions not approved by our board, the beneficial owner, directly or indirectly, of our securities representing more than 50% of the total voting power; (ii) a merger or consolidation has occurred, whether or not approved by our board, which results in the holders of our voting securities holding less than 50% of the combined voting power of the surviving entity immediately after such merger or consolidation; (iii) the sale or disposition of more than two-thirds of our assets; or (iv) the date a majority of members of our board is replaced during any 12-month period by directors whose appointment or election is not endorsed by a majority of members of the our board before the date of the appointment or election.

The benefits described above for Drs. Hecht and Dr. Currie and Mr. Huyett are only payable if the executive officer complies with all of our rules and policies, executes a separation agreement that includes a release of claims and complies with his post-employment obligations of non-disclosure, non-competition and non-solicitation. The severance agreements further provide that in connection with the sale of all or substantially all of the assets of the Company, we will cause the acquirer of such assets to assume the arrangements.

Outstanding Equity Awards at Fiscal Year-End

The following table sets forth information regarding Ironwood equity awards held by our named executive officers as of December 31, 2018.

	Option Awards					Stock Awards	
Name	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Equity Incentive Plan Awards: Number of Securities Underlying Unexercised Unearned Options (#)	Option Exercise Price ($)	Option Expiration Date	Number of Shares or Units of Stock That Have Not Vested (#)(1)	Market Value of Shares or Units of Stock That Have Not Vested ($)(2)
Peter M. Hecht, Ph.D	110,000	—	—	4.89	2/11/2019(3)	—	—
	20,000	—	20,000	5.48	7/28/2019(4)	—	—
	125,000	—	—	11.25	2/2/2020(3)	—	—
	175,000	—	—	11.11	2/1/2021(3)	—	—
	300,000	—	—	14.72	2/1/2022(3)	—	—
	375,000	—	—	13.08	2/1/2023(3)	—	—
	325,000	—	—	14.11	3/3/2024(5)	—	—
	553,229	11,771	—	15.62	3/16/2025(5)	—	—
	648,958	241,042	—	10.24	3/1/2026(5)	—	—
	364,166	395,834	—	16.77	2/27/2027(5)	—	—
	132,916	447,084	—	14.55	2/21/2028(5)	—	—
Mark G. Currie, Ph.D.	0	—	20,000	5.48	7/28/2019(4)	—	—
	8,888	—	—	11.25	2/2/2020(3)	—	—
	41,041	—	—	11.11	2/1/2021(3)	—	—
	110,000	—	—	14.72	2/1/2022(3)	—	—
	200,000	—	—	13.08	2/1/2023(3)	—	—
	85,000	—	—	14.11	3/3/2024(5)	—	—
	128,515	2,735	—	15.62	3/16/2025(5)	—	—
	25,000	—	25,000	15.62	3/16/2025(6)	—	—
	88,124	63,646	—	10.24	3/1/2026(5)	—	—
	119,791	130,209	—	16.77	2/27/2027(5)	—	—
	49,270	165,730	—	14.55	2/21/2028(5)	17,468	180,968
William Huyett	84,375	253,125	—	15.27	1/2/2028(7)	54,187	561,377

(1) The Ironwood restricted stock units vest over four years as to 25% of the award on each anniversary of the grant thereof.

(2) Market value is calculated by multiplying the number of Ironwood restricted stock units that have not vested by the closing price of Ironwood common stock on Nasdaq on December 31, 2018, which was $10.36.

(3) The Ironwood options vest as to 1.25% on each monthly anniversary of the vesting commencement date for the first 36 months, and as to 4.5833% of the award on each monthly anniversary thereafter until fully vested.

(4) The Ironwood options vested as to (a) 50% of the shares upon acceptance by the FDA of a second NDA for a product from an internal or external development program (excluding supplemental NDAs for linaclotide, but including NDAs for linaclotide combination products) and vest as to (b) 50% of the shares upon the achievement of $1 billion in annual (calendar year) net global pharmaceutical product sales (including partnered or licensed product revenue) for Ironwood. Ironwood external development programs shall be pre-qualified for milestone vesting eligibility by the Ironwood Compensation and HR Committee as of the time of program initiation at Ironwood.

(5) The Ironwood options vest as to 1/48th of the shares on each monthly anniversary of the vesting commencement date until fully vested.

(6) The Ironwood options vest in two equal installments of 25,000 options each. The option vested as to 25,000 shares upon the first-dosing in the first clinical study of the next phase following achievement of proof of concept for the first internally derived or externally accessed product (other than linaclotide) qualified by the Ironwood Compensation and HR Committee as targeting a new indication, category or market. The remaining 25,000 shares vest upon the first-dosing in the first clinical study of the next phase following achievement of proof of concept for the second internally derived or externally accessed product (other than linaclotide) qualified by the Ironwood Compensation and HR Committee as targeting a new indication, category or market.

(7) The Ironwood options vest as to 25% of the shares on the first anniversary of the vesting commencement date and 1/48th of the shares each month thereafter for the next 36 months.

Director Compensation

Dr. Hecht is not compensated for his service as a member of our board of directors, nor was he compensated for his service as a member of Ironwood's board of directors. Dr. Hecht's compensation for his service as Ironwood's chief executive officer is described above in the section of this prospectus entitled "Executive Compensation". The following table sets forth information concerning the compensation paid to, or awarded to, our directors, other than Dr. Hecht, under Ironwood's director compensation plan during fiscal year 2018:

Name	Fees Earned or Paid in Cash ($)	Stock Awards ($)(1)	Total ($)
Marsha H. Fanucci	10,000(2)	301,423	311,423
Terrance G. McGuire	9,965(3)	301,423	311,388
Amy W. Schulman	7,299(4)	301,423	308,722

(1) On May 31, 2018, each non-employee member of Ironwood's board of directors was granted a restricted stock award in the amount of 16,223 shares of Ironwood's Class A common stock for service to Ironwood from the date of Ironwood's 2018 annual meeting of stockholders to the date of Ironwood's 2019 annual meeting of stockholders. The amount of this restricted stock grant was determined by dividing (i) $250,000 (the dollar amount for total director compensation approximating the 25th percentile of Ironwood's current peer group on the date of grant), by (ii) the average closing price of Ironwood's Class A common stock on Nasdaq for the six months preceding the month of the 2018 annual meeting of stockholders. Such award of restricted stock had a grant date fair value of $18.58 per share and was granted pursuant to the terms of Ironwood's director compensation plan. As of December 31, 2018, 8,112 shares from each such restricted stock award remained unvested.

(2) Ms. Fanucci received this compensation for her service as the chair of Ironwood's audit committee in 2018.

(3) Mr. McGuire received this compensation for his service as the chair of Ironwood's board for 2018. Pursuant to Ironwood's director compensation plan, Mr. McGuire elected to receive this compensation in unrestricted shares of Ironwood's Class A common stock. Mr. McGuire received a total of 645 shares of Ironwood's Class A common stock for such chair service in 2018.

(4) Ms. Schulman received this compensation for her service as the chair of Ironwood's capital allocation committee for a portion of 2018. Pursuant to Ironwood's director compensation plan, Ms. Schulman elected to receive this compensation in unrestricted shares of Ironwood's Class A common stock. Ms. Schulman received a total of 474 shares of Ironwood's Class A common stock for such chair service in 2018.

As discussed in the section of this prospectus entitled "Employee Matters Agreement—Equity Compensation," any of our non-employee directors who served as non-employee directors of Ironwood received shares of our unvested restricted stock in respect of any outstanding unvested awards of Ironwood restricted stock they held. Such restricted stock awards are subject to the vesting schedule set forth in the original Ironwood restricted stock award. On April 1, 2019, we made grants of our restricted stock to our non-employee directors who did not hold Ironwood restricted stock prior to the distribution. Such restricted stock awards have an equivalent value to the shares of our restricted stock granted to our non-employee directors who held Ironwood restricted stock prior to the distribution, and have been pro-rated to reflect each non-employee director's period of service with us from the date of the distribution to the anticipated date of the first annual grant.

2019 Compensation Plans

We have adopted (i) the Cyclerion Therapeutics, Inc. 2019 Equity Incentive Plan, or our 2019 Equity Plan; and (ii) the Cyclerion Therapeutics, Inc. 2019 Employee Stock Purchase Plan, or our 2019 ESPP. We refer to these plans collectively as our "2019 Plans." The following summaries describe the material terms of our 2019 Plans. These summaries are not complete descriptions of all of the terms of our 2019 Plans and are qualified in their entirety by reference to our 2019 Plans, which have been filed as exhibits to the registration statement of which this prospectus is a part.

2019 Equity Plan

In General

Our 2019 Equity Plan provides for the grant of stock and stock-based awards. The purpose of our 2019 Equity Plan is to advance the interests of the Company by providing for the grant to participants of incentive equity awards. Awards granted under our 2019 Equity Plan are intended to be eligible for the post-initial public offering transition relief under Section 162(m) of the Code, as set forth in Section 1.162-27(f) of the Treasury Regulations.

Administration

Our 2019 Equity Plan is generally administered by our compensation committee, which has the discretionary authority to interpret the plan; determine eligibility for and grant awards; determine, modify and waive the terms and conditions of any award; determine the form of settlement of awards; prescribe forms, rules and procedures relating to the plan and awards; and otherwise do all things necessary or desirable to carry out the purposes of the plan. Our compensation committee may delegate to one or more of its members or members of our board of directors such of its duties, powers, and responsibilities as it may determine and, to the extent permitted by law, may delegate its ministerial tasks to employees and other persons as it deems appropriate. As used in this summary, the term "Administrator" refers to our compensation committee or its authorized delegates, as applicable.

Eligibility

Our and our subsidiaries' employees, directors, consultants and advisors are eligible to participate in our 2019 Equity Plan. Eligibility for stock options intended to be incentive stock options, or ISOs, is limited to our employees and employees of certain qualifying subsidiaries. Eligibility for stock options other than ISOs and stock appreciation rights, or SARs, is limited to individuals who are providing direct services on the date of grant of the award to us or certain qualifying subsidiaries. As of April 1, 2019, approximately 143 employees, 8 directors and certain consultants and advisors are eligible to participate in our 2019 Equity Plan, including all of our executive officers.

Authorized Shares

Subject to adjustment as described below, the number of shares of our common stock that may be issued in satisfaction of awards under our 2019 Equity Plan is initially 2,500,000 shares, plus (1) an automatic increase, as of the date of each annual meeting of our shareholders, from the first annual meeting until the ninth annual meeting, of a number of shares equal to the lesser of (A) four percent (4%) of the number of outstanding shares of our common stock as of the close of business on the immediately preceding business day, and (B) the number of shares determined by the Administrator on or prior to the date of such annual meeting of shareholders and (2) any shares underlying awards granted under our 2005 Plan or our 2010 Plan are forfeited, expired or are cancelled without the delivery of shares of common stock thereunder. Up to the total number of shares of our common stock set forth in the preceding sentence may be issued in satisfaction of ISOs. The number of shares of common stock issued in satisfaction of awards under our 2019 Equity Plan will be determined by excluding (i) the shares of common stock withheld by us in payment of the exercise or purchase price or an award or in satisfaction of tax withholding requirements, (ii) the number of shares covered by a SAR, any portion of which is settled in common stock, and (iii) any shares underlying any portion of an award that is settled or that expires, becomes unexercisable, terminates or is forfeited to or repurchased by us without the issuance of stock. The number of shares available for delivery under the 2019 Equity Plan will not increase by any number of shares that are delivered and subsequently repurchased using proceeds directly attributable to stock option exercises.

Shares that may be issued under our 2019 Equity Plan may be authorized but unissued shares, treasury shares or previously issued shares acquired by us.

Individual Limits

Awards comprising no more than 1,000,000 shares of our common stock may be granted to any participant in any calendar year. In applying the individual limit, all shares subject to stock options that may be granted, all shares subject to SARs that may be granted, and all shares subject to awards other than stock options and SARs that may be granted will be aggregated and made subject to a single limit.

Director Limits

In addition to the individual limits described above, the aggregate value of all compensation granted or paid to any non-employee director with respect to any calendar year for his or her services as a director, including awards under our 2019 Equity Plan, for his or her services as a director during such calendar year may not exceed $400,000, with the value of any awards under our 2019 Equity Plan calculated based on the grant date fair value and assuming maximum payout.

Types of Awards

Our 2019 Equity Plan provides for the grant of stock options, SARs, restricted and unrestricted stock and stock units, performance awards, and other awards that are convertible into or otherwise based on our common stock. Dividend equivalents may also be provided in connection with awards under our 2019 Equity Plan.

- *Stock Options and SARs.* The Administrator may grant stock options, including ISOs, and SARs. A stock option is a right entitling the holder to acquire shares of our common stock upon payment of the applicable exercise price. A SAR is a right entitling the holder upon exercise to receive an amount (payable in cash or shares of equivalent value) equal to the excess of the fair market value of the shares subject to the right over the base value from which appreciation is measured. The per share exercise price of each stock option, and the per share base value of each SAR, granted under our 2019 Equity Plan may not be less than 100% of the fair market value of a share of our common stock on the date of grant (or 110% in the case of ISOs

granted to any employee who holds 10% or more of the total combined voting power of our stock).

- *Restricted and Unrestricted Stock and Stock Units.* The Administrator may grant awards of stock, stock units, restricted stock and restricted stock units. A stock unit is an unfunded and unsecured promise, denominated in shares, to deliver shares or cash measured by the value of shares in the future, and a restricted stock unit is a stock unit that is subject to the satisfaction of specified performance or other vesting conditions. Restricted stock is stock subject to restrictions requiring that it be forfeited, redelivered or offered for sale to us if specified performance or other vesting conditions are not satisfied.

- *Performance Awards.* The Administrator may grant performance awards, which are awards subject to performance vesting conditions, including the performance criteria described below.

- *Other Stock- Based Awards.* The Administrator may grant other awards that are convertible into or otherwise based on shares of our common stock, subject to such terms and conditions as are determined by the Administrator.

- *Substitute Awards.* The Administrator may grant awards in substitution for equity awards of an acquired company, which may have terms and conditions that are inconsistent with the terms and conditions of our 2019 Equity Plan.

Vesting; Terms and Conditions of Awards

The Administrator will determine the terms and conditions of all awards granted under our 2019 Equity Plan, including the time or times an award vests or becomes exercisable, the terms and conditions on which an option or SAR remains exercisable, and any modifications to the effect of termination of a participant's employment or service on awards from the terms set forth in our 2019 Equity Plan. The Administrator may at any time accelerate the vesting or exercisability of an award.

Transfer Restrictions

Except as the Administrator may otherwise determine, awards may not be transferred other than by will or by the laws of descent and distribution. ISOs may not be transferred other than by will or by the laws of descent and distribution.

Performance Criteria

Our 2019 Equity Plan provides for grants of performance awards subject to "performance criteria." Performance criteria may be applied to a participant individually, or to a business unit or division or the Company as a whole and may relate to any or any combination of the following or any other criteria determined by the Administrator (measured either absolutely or by reference to an index or indices or the performance of one or more companies) and determined either on a consolidated basis or, as the context permits, on a divisional, subsidiary, line of business, project or geographical basis or in combinations thereof): achievement of research, clinical trial or other drug development objectives; achievement of regulatory objectives; achievement of manufacturing and/or supply chain objectives; sales; revenues; assets; expenses; earnings before or after deduction for all or any portion of interest, taxes, depreciation, or amortization, whether or not on a continuing operations or an aggregate or per share basis; return on equity, investment, capital or assets; one or more operating ratios; borrowing levels, leverage ratios or credit rating; market share; capital expenditures; cash flow; stock price; shareholder return; sales of particular products or services; customer acquisition or retention; acquisitions and divestitures (in whole or in part); joint ventures, licenses and strategic alliances; spin-offs, split-ups and the like; reorganizations; recapitalizations, restructurings, financings (issuance of

debt or equity) or refinancings and may be adjusted by the Administrator during the applicable performance period to reflect events that affect the performance criteria.

Effect of Certain Transactions

In the event of certain covered transactions (including a consolidation, merger or similar transaction, a sale of substantially all of our assets or common stock, a change in control, or a dissolution or liquidation of the Company), the Administrator may, with respect to outstanding awards, provide for (in each case, on such terms and conditions as it determines):

- The assumption, continuation or substitution for some or all awards (or any portion thereof) by the acquirer or surviving entity;
- The acceleration of exercisability or delivery of shares in respect of any award (or any portion thereof), in full or in part; and/or
- The cash payment in respect of some or all awards (or any portion thereof) equal to the difference between the fair market value of the shares subject to the award and its exercise or base price, if any.

Except as the Administrator may otherwise determine, each award will automatically terminate immediately upon the consummation of the covered transaction, other than awards that are substituted for, assumed or continued.

Adjustment Provisions

In the event of a stock dividend, stock split or combination of shares (including a reverse stock split), recapitalization or other change in our capital structure, the Administrator will make appropriate adjustments to the maximum number of shares that may be issued under our 2019 Equity Plan, the individual limits described above, the number and kind of securities subject to, and, if applicable, the exercise or purchase prices (or base values) of, outstanding awards, and any other provisions affected by such event. The Administrator may also make such adjustments to take into account other distributions to shareholders or any other event if it determines that adjustments are appropriate to avoid distortion in the operation of our 2019 Equity Plan or any award.

Recovery of Compensation

The Administrator may provide that any outstanding award or the proceeds from, or other amounts received in respect of, any award or stock acquired under any award will be subject to forfeiture and disgorgement to us if the participant to whom the award was granted is not in compliance with any non-competition, non-solicitation, no-hire, non-disparagement, confidentiality, invention assignment or other restrictive covenant, or any of our applicable policies that provides for forfeiture or disgorgement, or as otherwise required by law or applicable stock exchange listing standards. In addition, the Administrator may require forfeiture or disgorgement to us of any outstanding award or the proceeds from, or other amounts received in respect of, any award or stock acquired under the award with interest or other related earnings, to the extent required by law or applicable stock exchange listings standards, including, without limitation, Section 10D of the Exchange Act.

Amendment and Termination

The Administrator may at any time amend our 2019 Equity Plan or any outstanding award and may at any time terminate our 2019 Equity Plan as to future grants. However, except as expressly provided in our 2019 Equity Plan or the applicable award, the Administrator may not alter the terms of an award so as to materially and adversely affect a participant's rights without the participant's consent,

unless the Administrator expressly reserved the right to do so at the time the award was granted. Any amendments to our 2019 Equity Plan will be conditioned on shareholder approval to the extent required by law or applicable stock exchange requirements.

2019 ESPP

In General

Our 2019 ESPP is intended to enable eligible employees to use payroll deductions to purchase shares of our common stock, and thereby acquire an interest in our future. Our 2019 ESPP will generally be implemented by a series of separate offerings, which we refer to as offering periods. On the first day of each offering period, participating employees will be granted an option to purchase shares of our common stock, which will be automatically exercised on the last business day of the offering period. Our 2019 ESPP is intended to satisfy the requirements of Section 423 of the Code. As of the date of this prospectus, no options to purchase shares of our common stock have been granted under our 2019 ESPP.

Administration

Our 2019 ESPP is administered by our compensation committee, which has the authority to interpret the plan; determine eligibility under the plan; prescribe forms, rules and procedures relating to the plan; and otherwise do all things necessary or appropriate to carry out the purposes of the plan. Our compensation committee may delegate to one or more of its members or members of our board of directors such of its duties, powers, and responsibilities as it may determine and may delegate such ministerial tasks as it deems appropriate to employees or other persons. As used in this summary, the term "Administrator" refers to our compensation committee or its authorized delegates, as applicable.

Eligibility

Participation in our 2019 ESPP is generally limited to our and our participating subsidiaries' employees (i) who have been continuously employed by us or our subsidiary, as applicable, for a period of at least fifteen business days as of the first day of an applicable offering period; (ii) whose customary employment with us or our subsidiary, as applicable, is for more than five months per calendar year; (iii) who customarily work 20 hours or more per week; and (iv) who satisfy the requirements set forth in our 2019 ESPP. The Administrator may establish additional or different eligibility requirements to the extent consistent with Section 423 of the Code. No employee may be granted an option under our 2019 ESPP if, immediately after the option is granted, the employee would own (or would be deemed to own) shares of our common stock possessing five percent or more of the total combined voting power or value of all classes of shares of the Company or of our parent or subsidiaries, if any. As of April 1, 2019, approximately 143 employees are eligible to participate in our 2019 ESPP, including all of our executive officers.

Authorized Shares

Subject to adjustment as described below, the maximum aggregate number of shares of our common stock that are available for issuance under our 2019 ESPP is initially 400,000 shares, which number will increase as of the date of each annual meeting of our shareholders, from the first annual meeting of the shareholders following the adoption of the ESPP until the ninth annual meeting following the adoption of the ESPP. Such annual increase will be equal to the lesser of (A) one percent of shares of stock outstanding on a fully diluted basis as of the close of business on the immediately preceding day, and (B) the number of shares determined by the Administrator on or prior to such date. Shares that may be issued under our 2019 ESPP may be authorized but unissued shares, shares of treasury stock or previously issued shares acquired by us. If any option expires or terminates for any

reason without having been exercised in full or ceases for any reason to be exercisable in whole or in part, the unpurchased shares subject to such option will again be available for purchase under the plan.

Participation

Eligible employees may participate in an offering period under our 2019 ESPP by delivering a payroll deduction and participation authorization form to the Administrator, authorizing a whole percentage of the employee's eligible compensation, between one percent and 15 percent of the employee's eligible compensation, to be deducted from the employee's pay during the offering period. The payroll deduction authorization must be delivered no later than 15 business days prior to the first day of the offering period (or such other period specified by the Administrator). A payroll deduction authorization under our 2019 ESPP will remain in effect for subsequent offering periods unless a participant delivers a new payroll deduction authorization or the participant's participation in our 2019 ESPP is terminated.

Offering Periods

Unless otherwise determined by the Administrator, offering periods under our 2019 ESPP will be six months in duration and commence on the first business day of June and December of each year.

Subject to the limitations in our 2019 ESPP, as described in this summary, on the first day of each offering period, participating employees will be granted an option to purchase shares of our common stock, except that no participant will be granted an option under our 2019 ESPP that permits the participant's right to purchase shares of our common stock under our 2019 ESPP and under all of our other employee stock purchase plans or subsidiaries' employee stock purchase, if any, to accrue at a rate that exceeds $25,000 in fair market value (or such other maximum as may be prescribed by the Code) for each calendar year during which any option granted to the participant is outstanding at any time, determined in accordance with Section 423 of the Code.

Each option to purchase shares of our common stock granted under our 2019 ESPP for an offering period, unless earlier cancelled, will be automatically exercised on the last business day of the offering period. Upon exercise, shares will be purchased using the participant's accumulated payroll deductions for the offering period, which will be maintained on our books in a notional account. A participant may purchase a maximum of 2,500 shares of our common stock with respect to any offering period (or such lesser number of shares as the Administrator may prescribe).

Purchase Price

The purchase price of each share issued pursuant to the exercise of an option under our 2019 ESPP on an exercise date will be 85% (or such greater percentage as specified by the Administrator) of the lesser of (i) the fair market value of a share on date the option is granted and (ii) the fair market value of a share on the exercise date.

Changes to Payroll Authorization; Termination

During an offering period, a participant may decrease his or her payroll deduction authorization once (including to zero) while continuing to participate in our 2019 ESPP, but may not increase his or her payroll deduction authorization.

A participant may cancel his or her enrollment and terminate his or her payroll deduction authorization by delivering a notice to the Administrator at least 15 business days prior to the exercise date. Upon termination of a participant's employment prior to an exercise date for an offering period, or if a participant ceases to be eligible to participate in the plan, or in the case of the death of a participant during an offering period, the participant's option will be cancelled automatically. Upon cancellation, the balance of the participant's account will be returned to the participant, without interest, as soon as administratively practicable.

Holding Period

For participants who have purchased shares under our 2019 ESPP, the Administrator may impose restrictions prohibiting the transfer, sale, pledge or alienation of such shares, other than by will or by the laws of descent and distribution, for such period as may be determined by the Administrator.

Effect of Certain Transactions

In the event a sale of substantially all of our assets or common stock, or merger or similar transaction in which we are not the surviving corporation or that results in our acquisition by another person, the Administrator may (i) if we are merged with or acquired by another corporation, provide that each outstanding option will be assumed or exchanged for a substitute option; (ii) cancel each outstanding option and return the balances in the participants' accounts, without interest; and/or (iii) terminate the offering period on or before the date of the proposed sale, merger or similar transaction.

Adjustment Provisions

In the event of any change in the outstanding stock by reason of a stock dividend, stock split, reverse stock split, split-up, recapitalization, merger, consolidation, reorganization, or other capital change, the Administrator will make appropriate adjustments to the aggregate number and type of shares available for purchase under our 2019 ESPP, the maximum number and type of shares purchasable under any outstanding option and/or the purchase price under any outstanding option, provided that such change complies with Section 423 of the Code.

Amendment and Termination

The Administrator has the discretion to change the commencement and exercise dates of offering periods, the purchase price, the maximum number of shares that may be purchased with respect to any offering period, the duration of any offering periods and other terms of our 2019 ESPP, in each case, without shareholder approval, in a manner consistent with Section 423 of the Code and in order to, among other things, reflect the impact of local law outside of the United States as applied to one or more eligible employees of a Company subsidiary, and the Administrator may, where appropriate, establish one or more sub-plans to reflect such amended provisions.

Our board of directors may at any time amend, suspend or terminate our 2019 ESPP, provided that any amendment that would be treated as the adoption of a new plan for purposes of Section 423 of the Code will require shareholder approval.

2010 and 2005 Plans

Prior to the distribution, our board of directors adopted (i) the Cyclerion Therapeutics, Inc. Amended and Restated 2010 Employee, Director and Consultant Equity Incentive Plan, or our 2010 Plan, and (ii) the Cyclerion Therapeutics, Inc. Amended and Restated 2005 Stock Incentive Plan, or our 2005 Plan. We refer to these plans collectively as our "Mirror Plans." Our Mirror Plans are intended to mirror in all material respects the terms and conditions of the Ironwood Pharmaceuticals, Inc. Amended and Restated 2010 Employee, Director and Consultant Equity Incentive Plan, or the Ironwood 2010 Plan, and the Ironwood Pharmaceuticals, Inc. Amended and Restated 2005 Stock Incentive Plan, or the Ironwood 2005 Plan, for purposes of governing awards previously issued under the Ironwood 2010 Plan and the Ironwood 2005 Plan, respectively, that were converted into awards in respect of our common stock pursuant to the terms of the employee matters agreement. No awards will be made under the Mirror Plans. The following summaries describe the material terms of our Mirror Plans. These summaries are not complete descriptions of all of the terms

of our Mirror Plans and are qualified in their entirety by reference to our Mirror Plans, which have been filed as exhibits to the registration statement of which this prospectus is a part.

2010 Plan

Our 2010 Plan provides for the grant of stock and stock-based awards. Subject to adjustment, the maximum number of shares of our common stock that may be issued pursuant to awards is 8,200,000 shares. In the event that an outstanding award expires, is cancelled or otherwise terminated without consideration, such shares will be available for grant under our 2019 Equity Plan. As of April 1, 2019, options to purchase approximately 6,242,203 shares of our common stock, approximately 932,469 restricted stock units and approximately 9,837 shares of restricted stock were outstanding under our 2010 Plan.

Our 2010 Plan is generally be administered by our board of directors, which has discretionary authority to interpret the provisions of our 2010 Plan and to make any rules and determinations which it deems advisable for the administration of our 2010 Plan. To the extent permitted under applicable law, our board of directors may delegate to a committee, or to one or more of the members of our board of directors, its authority and duties under our 2010 Plan. As used in this summary, the term "Administrator" refers to our board of directors or its authorized delegates, as applicable.

Each of our named executive officers has been granted options to purchase Ironwood common stock and restricted stock units in respect of Ironwood common stock under the Ironwood 2010 Plan. Awards granted under the Ironwood 2010 Plan were adjusted as described in the section of this prospectus entitled "Employee Matters Agreement—Equity Compensation." Any awards granted under the Ironwood 2010 Plan that converted into awards under our 2010 Plan are subject to substantially the same terms and vesting conditions as were applicable to the award granted under the Ironwood 2010 Plan prior to the distribution.

In the event of a corporate transaction, generally defined in our 2010 Plan to include a transaction in which our company is to be consolidated with or acquired by another entity through a merger, consolidation or sale of all or substantially all of our assets, the Administrator will take, or cause to be taken, any of the following actions as to all or any outstanding stock options, on such terms as the Administrator determines, unless otherwise specifically provided by the terms of the stock option: (i) provide for the assumption of stock options by the acquiring or surviving entity, (ii) upon written notice, provide that unexercised stock options, with such options being made fully exercisable, must be exercised within a specified number of days, at the end of which period such stock options, if not exercised, shall terminate or (iii) provide for termination of unexercised stock options, with such stock options being made fully exercisable, in exchange for a cash payment to the holder of such stock options equal to the difference between the per share consideration received by common shareholders in the corporate transaction and the exercise price of each such stock option. With respect to outstanding awards other than stock options, the Administrator will make provision for the substitution of awards by the surviving or acquiring entity or for the termination of awards in exchange for payment in an amount equal to the consideration payable in the corporate transaction to a holder of the number of shares of common stock comprising such awards.

Our shareholders, and in certain instances, the Administrator, may amend our 2010 Plan at any time. However, no such action may adversely affect any rights under any outstanding award without the participant's consent.

2005 Plan

Our 2005 Plan provides for the grant of stock and stock-based awards. Subject to adjustment, the maximum number of shares of our common stock that may be issued pursuant to awards is 250,000 shares. In the event that an outstanding award expires, is cancelled or otherwise terminated without

consideration, such shares will be available for grant under our 2019 Equity Plan. As of April 1, 2019 options to purchase approximately 214,779 shares of our common stock were outstanding under our 2005 Plan.

Our 2005 Plan is generally administered by our board of directors, which has discretionary authority to adopt, amend and repeal administrative rules, guidelines and practices it deems advisable, and to correct any defect, supply any omission or reconcile any inconsistency in our 2005 Plan or an award granted under our 2005 Plan. To the extent permitted under applicable law, our board of directors may delegate to a committee its authority and duties under our 2005 Plan. As used in this summary, the term "Administrator" refers to our board of directors or its authorized delegates, as applicable.

Drs. Hecht and Currie were granted options to purchase Ironwood common stock under the Ironwood 2005 Plan. Awards granted under the Ironwood 2005 Plan were adjusted as described in the section of this prospectus entitled "Employee Matters Agreement—Equity Compensation." Any awards granted under the Ironwood 2005 Plan converted into awards under our 2005 Plan are subject to substantially the same terms and vesting conditions as were applicable to the award granted under the Ironwood 2005 Plan prior to the distribution.

In the event of a reorganization event, generally defined in our 2005 Plan to include any merger or consolidation of our company into another entity, any exchange of all of our common stock for cash, securities or other property pursuant to a share exchange transaction or any liquidation or dissolution of our company, the Administrator will take, or cause to be taken, any of the following actions as to all or any outstanding awards, as determined by the Administrator: (i) provide for the assumption or substitution of awards by the acquiring or surviving entity, (ii) upon written notice, provide that unexercised stock options, or other unexercised awards, with such awards being made fully exercisable, must be exercised within a specified number of days, at the end of which period such stock options, if not exercised, shall terminate, (iii) provide that outstanding awards shall become realizable or deliverable, or restrictions applicable to an award shall lapse, in whole or in part prior to or upon the reorganization event, (iv) in the event of a reorganization event under the terms of which holders of our common stock will receive a cash payment for each share surrendered, provide for a cash payment in respect of some or all awards (or any portion thereof) equal to the difference between the fair market value of the shares subject to the award and its exercise or base price, if any, (v) provide that, in connection with a liquidation or dissolution of our company, awards shall convert into the right to receive liquidation proceeds (if applicable, net of the exercise price or base price thereof).

Our board of directors may amend our 2005 Plan at any time.

CERTAIN RELATIONSHIPS AND RELATED PERSON TRANSACTIONS

Relationship with Ironwood

Prior to the completion of the separation, all of our outstanding shares of common stock were owned by Ironwood. Following the completion of the separation, Ironwood no longer owns any shares of our common stock. See "Risk Factors—Risks Related to the Separation and the Private Placement."

Following the completion of the separation and the distribution, we and Ironwood have operated separately, each as an independent public company. In connection with the separation, we and Ironwood entered into certain agreements pursuant to which the separation of our business from Ironwood was effected and that govern our relationship with Ironwood going forward. The following is a summary of the terms of the material agreements that we entered into with Ironwood in connection with the separation, which have been filed as exhibits to the registration statement of which this prospectus is a part. These summaries set forth the terms of the agreements that we believe are material and are qualified in their entirety by reference to the full text of such agreements.

Agreements with Ironwood

Separation Agreement

We entered into a separation agreement with Ironwood dated March 30, 2019, which sets forth our agreements with Ironwood regarding the principal actions taken in connection with the separation, including the distribution. The separation agreement identifies the assets transferred, liabilities assumed and contracts assigned to each of us and Ironwood as part of the separation, and sets forth when and how these transfers, assumptions and assignments occurred.

Transfer of Assets and Assumption of Liabilities. The separation agreement identifies the assets transferred, liabilities assumed, and contracts assigned to each of Ironwood and us, and provides for the transfer of such assets, assumption of such liabilities and assignment of such contracts. Following the completion of the separation and the distribution, we and Ironwood have the assets necessary to operate our respective businesses and retain or assume the liabilities related to those assets. The separation agreement also provides for the settlement or extinguishment of certain liabilities and other obligations between us and Ironwood.

The allocation of liabilities with respect to taxes, except for payroll tax withholding and reporting and other tax matters expressly covered by the employee matters agreement, are solely covered by the tax matters agreement.

Employee Non-Solicit and Non-Hire. Pursuant to the separation agreement, we and Ironwood are each subject to mutual two-year employee non-solicitation and non-hire obligations, subject to customary exceptions.

Certain Restrictions. Pursuant to the separation agreement, we and Ironwood, as well as our and Ironwood's respective affiliates, are subject to non-compete restrictions, subject to customary carve-outs for performance under the separation agreement, acquisitions of entities engaged in a restricted business and an acquirer's commercially available products and product candidates in clinical development at the time of the acquisition. Until April 1, 2022, three years after the distribution date, Ironwood is prohibited from engaging in the business of discovering, researching, developing, importing, exporting, manufacturing, marketing, distributing, promoting or selling any pharmaceutical product (a) for the diagnosis, prevention or treatment of DN, HFpEF or SCD, or (b) that contains one or more sGC stimulators. Until April 1, 2029, 10 years after the distribution date, we are prohibited from engaging in the business of discovering, researching, developing, importing, exporting, manufacturing, marketing, distributing, promoting or selling any pharmaceutical product for the diagnosis, prevention or treatment of irritable bowel syndrome, constipation or gastroesophageal reflux

disease. In addition, until April 1, 2022, three years after the distribution date, we are prohibited from engaging in the business of discovering, researching, developing, importing, exporting, manufacturing, marketing, distributing, promoting or selling any pharmaceutical product (x) for the diagnosis, prevention or treatment of GI diseases or disorders (provided that this restriction only applies to functional dyspepsia, functional vomiting and functional diarrhea with respect to an acquirer of us following a change of control) other than irritable bowel syndrome, constipation or gastroesophageal reflux disease, except with respect to the use of an sGC as the primary active ingredient, (y) for the diagnosis, prevention or treatment of diseases or disorders with the recognized signs or symptoms of visceral, abdominal or pelvic pain, except with respect to the use of an sGC as the primary active ingredient for the diagnosis, prevention or treatment of an indication other than endometriosis and bladder pain syndrome, or (z) that contains one or more guanylate cyclase-C agonists or is or contains any bile sequestrant-based therapy, in each case except for the use of guanylate cyclase-C agonists in an injectable product for the diagnosis, prevention or treatment of indications other than GI diseases and disorders with the prior written consent of Ironwood.

Indemnification. The separation agreement provides for releases, with respect to pre-distribution claims, and cross-indemnities, with respect to post-distribution claims, that, except as otherwise provided in the separation agreement, are principally designed to place financial responsibility for the obligations and liabilities allocated to us under the separation agreement with us and financial responsibility for the obligations and liabilities allocated to Ironwood under the separation agreement with Ironwood. The separation agreement also specifies procedures with respect to claims subject to indemnification and related matters. Indemnification with respect to taxes is governed by the tax matters agreement described below.

Term/Termination. After the distribution date, the separation agreement may only be terminated, modified or amended with the prior written consent of both Ironwood and us.

Other Matters Governed by the Separation Agreement. Other matters governed by the separation agreement include, without limitation, access to financial and other information, insurance, confidentiality and access to and provision of records and the rights and obligations of the parties with respect to the distribution.

Development Agreement

We entered into a development agreement with Ironwood dated April 1, 2019 pursuant to which we are required to provide Ironwood with certain research and development services with respect to certain of Ironwood's products and product candidates, including without limitation MD-7246 (linaclotide delayed release) and IW-3718. Such research and development activities will be governed by a joint steering committee comprised of our representatives and representatives from Ironwood. Ironwood will pay us fees for such research and development services, which fees will be mutually agreed upon by us and Ironwood as provided under the development agreement with certain allowances for specified overages.

Transitional Services Agreements

Ironwood Transitional Services. Historically, Ironwood has provided us significant corporate and shared services and resources related to corporate functions such as finance, human resources, internal audit, research and development, financial reporting and information technology, which we refer to collectively as the "Ironwood Services." The Ironwood transitional services agreement with us dated April 1, 2019 became operative as of the completion of the separation and each of the Ironwood Services will continue for an initial term of between three months to eighteen months (as applicable), unless earlier terminated or extended according to the terms of the Ironwood transitional services agreement. We have agreed to pay Ironwood fees for the Ironwood Services, to be mutually agreed

upon by us and Ironwood as provided under the Ironwood transitional services agreement, which fees will be based on Ironwood's cost of providing the Ironwood Services.

Cyclerion Transitional Services. We also entered into a second transitional services agreement with Ironwood dated April 1, 2019 whereby we have agreed to provide certain finance, procurement and facilities services to Ironwood, which we refer to collectively as the "Cyclerion Services." This second transitional services agreement became effective as of the completion of the separation and each of the Cyclerion Services will continue for an initial term of one year, unless earlier terminated or extended according to the terms of the Cyclerion transitional services agreement. Ironwood has agreed to pay us fees for the Cyclerion Services, to be mutually agreed upon by us and Ironwood as provided under the Cyclerion transitional services agreement, which fees will be based on our cost of providing the Cyclerion Services.

Intellectual Property License Agreement

We entered into an intellectual property license agreement with Ironwood dated April 1, 2019 pursuant to which each party has agreed to grant to the other party a license to certain know-how. Ironwood granted us a perpetual, worldwide, non-exclusive, royalty-free, fully paid-up license to certain know-how to allow us to use such know-how in connection with our ongoing and future research and development activities related to sGC stimulator products in any field. We granted Ironwood a perpetual, worldwide, non-exclusive, royalty-free, fully paid-up license to certain know-how for use outside of the research and development of sGC stimulator products, including in Ironwood's existing products and product candidates. The licenses between the parties generally allow current or future uses of the know-how in connection with each party's respective fields.

Tax Matters Agreement

Allocation of taxes. We entered into a tax matters agreement with Ironwood dated March 30, 2019 which governs Ironwood's and our respective rights, responsibilities and obligations with respect to taxes (including taxes arising in the ordinary course of business and taxes, if any, incurred as a result of any failure of the distribution and certain related transactions to qualify as tax-free for U.S. federal income tax purposes), tax attributes, the preparation and filing of tax returns, the control of audits and other tax proceedings and assistance and cooperation in respect of tax matters. In general, under the agreement:

- Ironwood is responsible for any U.S. federal, state, local or foreign taxes (and any related interest, penalties or audit adjustments and including those taxes attributable to our business) reportable on a consolidated, combined or unitary return that includes Ironwood or any of its subsidiaries (and us and/or any of our subsidiaries) for any periods or portions thereof ending on or prior to April 1, 2019. We are responsible for the portion of any such taxes for periods or portions thereof beginning after such date, as would be applicable to us and/or any of our subsidiaries if it filed the relevant tax returns on a standalone basis.

- We are responsible for any U.S. federal, state, local or foreign taxes (and any related interest, penalties or audit adjustments) that are reportable on returns that include only our and/or any of our subsidiaries, for all tax periods whether before or after the completion of the distribution.

- Ironwood is responsible for certain taxes, if any, imposed on Ironwood and/or any of its subsidiaries and us and/or any of our subsidiaries arising from, or attributable to, certain transfers of assets or liabilities in the separation.

We are not generally entitled to receive payment from Ironwood in respect of any of our tax attributes or tax benefits or any reduction of taxes of Ironwood. Neither party's obligations under the tax matters agreement are limited in amount or subject to any cap. The tax matters agreement also

assigns responsibilities for administrative matters, such as the filing of returns, payment of taxes due, retention of records and conduct of audits, examinations or similar proceedings. In addition, the tax matters agreement provides for cooperation and information sharing with respect to tax matters.

Ironwood is primarily responsible for preparing and filing any tax return with respect to the Ironwood affiliated group for U.S. federal income tax purposes and with respect to any consolidated, combined, unitary or similar group for U.S. state or local or foreign tax purposes that includes Ironwood or any of its subsidiaries (including those that also include us and/or any of our subsidiaries), as well as any tax return that includes only Ironwood and/or any of its subsidiaries (including such tax returns that reflect taxes attributable to our business). We are generally responsible for preparing and filing any tax returns that include only us and/or any of our subsidiaries.

Ironwood generally has exclusive authority to control tax contests with respect to joint tax returns and tax returns that include only Ironwood and/or any of its subsidiaries. We generally have exclusive authority to control tax contests with respect to tax returns that include only us and/or any of our subsidiaries. The non-controlling party will generally have participation rights with respect to any tax contests to the extent the non-controlling party may be liable for any taxes pursuant to such tax contest.

Preservation of the tax-free status of certain aspects of the separation. The tax matters agreement imposes certain restrictions on us and our subsidiaries (including restrictions on share issuances, business combinations, sales of assets and similar transactions) designed to preserve the tax-free status of the distribution and certain related transactions. The tax matters agreement provides special rules that allocate tax liabilities in the event the distribution, together with certain related transactions, is not tax-free. In general, under the tax matters agreement, each party is responsible for any taxes imposed on Ironwood or us that arise from the failure of the distribution, together with certain related transactions, to qualify as a transaction that is generally tax-free, for U.S. federal income tax purposes, under Sections 355 and 368(a)(1)(D) and certain other relevant provisions of the Code, to the extent that the failure to so qualify is attributable to an acquisition of stock or assets of, or certain actions, omissions or failures to act of, such party. If both we and Ironwood are responsible for such failure, liability will be shared according to relative fault. If neither we nor Ironwood is responsible for such failure, Ironwood will generally bear any resulting taxes, interest, penalties and other costs.

We have agreed to certain covenants that contain restrictions intended to preserve the tax-free status of the distribution and certain related transactions. We may take certain actions prohibited by these covenants only if we obtain and provide to Ironwood either (i) a private letter ruling from the IRS or (ii) an opinion from a U.S. tax counsel or accountant of recognized national standing, in either case reasonably acceptable to Ironwood, to the effect that such action would not jeopardize the tax-free status of these transactions. We are barred from taking any action, or failing to take any action, where such action or failure to act adversely affects or could reasonably be expected to adversely affect the tax-free status of these transactions, for all time periods. In addition, during the time period ending April 1, 2021, two years after the date of the distribution, these covenants include specific restrictions on our:

- entering into any other corporate transaction which would cause us to undergo a 3% or greater change in its stock ownership, exclusive of the private placement;
- liquidating or partially liquidating, or merging or consolidating (unless we are the survivor);
- making or changing any entity classification election;
- ceasing to be engaged in an active trade or business, or selling, transferring or disposing of 25% or more of the net or gross assets of any active trade or business;
- amending any of our organizational documents or taking any action affecting the voting rights of our capital stock; and

- redeeming or otherwise repurchasing any of our outstanding stock or options.

We have generally agreed to indemnify Ironwood and its affiliates against any and all tax-related liabilities incurred by them relating to the distribution, including for any taxes, interest, penalties and other costs, including any reductions in Ironwood's net operating losses or other tax assets, to the extent caused by an acquisition of our stock or assets or certain actions by us. This indemnification provision applies even if Ironwood has permitted us to take an action that would otherwise have been prohibited under the tax-related covenants described above.

Employee Matters Agreement

We entered into an employee matters agreement with Ironwood dated March 30, 2019 which allocates assets, liabilities and responsibilities relating to the employment, compensation, and employee benefits of Ironwood and our employees, and other related matters in connection with the separation, including the treatment of outstanding incentive equity awards and certain retirement and welfare benefit obligations. The employee matters agreement generally provides that, unless otherwise specified, we are responsible for liabilities associated with employees who transferred to us and former employees of Ironwood whose employment terminated prior to the distribution but who primarily supported our business, whether incurred prior to or after the distribution, and Ironwood is responsible for liabilities associated with other employees, including employees retained by Ironwood.

Cyclerion 401(k) Plan

Pursuant to the employee matters agreement, we have adopted a defined contribution 401(k) plan, which is substantially similar in all material respects to Ironwood's 401(k) plan. The assets and liabilities under the Ironwood 401(k) plan with respect to our employees were transferred to the Cyclerion 401(k) plan.

Cyclerion Health and Welfare Plans

Pursuant to the employee matters agreement, we established health and welfare plans that correspond to the Ironwood health and welfare plans in which our employees participated immediately prior to the distribution. Our employees have been eligible to participate in our health and welfare plans since April 1, 2019. Ironwood has agreed to generally retain liability for claims incurred under Ironwood's health and welfare plans for our employees prior to the distribution. We have agreed to generally assume liability for claims incurred under Ironwood's health and welfare plans for our employees following the distribution.

There are no preexisting condition limitations under our health and welfare plans and our medical plan honors any deductibles incurred by our employees under an Ironwood medical plan during the portion of the calendar year prior to the distribution for purposes of satisfying deductibles and out-of-pocket maximums.

Cyclerion Omnibus Plan; Cyclerion Employee Stock Purchase Plan

Pursuant to the employee matters agreement, we adopted an omnibus equity incentive plan and an employee stock purchase plan intended to meet the requirements of Section 423 of the Internal Revenue Code of 1986, as amended (the "Code") and the regulations promulgated thereunder.

Equity Compensation

The employee matters agreement provides that outstanding Ironwood equity awards held by our and Ironwood employees adjusted as follows:

- For our and Ironwood employees, except as noted below, vested Ironwood equity awards converted into equity awards of both Ironwood and us using the "basket approach" (as described below).
- For our employees, except as noted below, unvested Ironwood equity awards converted into Cyclerion equity awards using the "concentration approach" (as described below).
- For Ironwood employees, unvested Ironwood equity awards remained as Ironwood equity awards using the "concentration approach."
- For our non-employee directors who had been non-employee directors of Ironwood, unvested Ironwood restricted stock converted into our unvested restricted stock using the "concentration approach."
- For non-employee directors of Ironwood who remain non-employee directors of Ironwood, unvested Ironwood restricted stock remained as unvested Ironwood restricted stock, adjusted using the "concentration approach."
- With respect to adjustments that resulted in fractional interests in shares, the fractional interests were rounded down to the nearest whole share and we or Ironwood, as the case may be, made or will make cash payments to our respective employees in lieu of such fractional interests.

Basket Approach. The number of shares underlying our converted equity awards (whether held by Ironwood or our employees) was determined according to a fixed ratio of one share of our common stock for every 10 shares of Ironwood common stock. The exercise price associated with our converted equity awards (whether held by Ironwood or our employees) was determined according to formulas based on $13.452, the 10-day volume weighted average trading price of Ironwood common stock for the 10 days immediately preceding the distribution and $14.809, the purchase price paid for our common stock in the private placement.

Concentration Approach. The number of shares underlying our converted equity awards and associated exercise prices was determined according to formulas based on $13.452, the 10-day volume weighted average trading price of Ironwood common stock for the 10 days immediately preceding the distribution and $14.809, the purchase price paid for our common stock in the private placement.

The following table contains a summary of the treatment of each type of Ironwood equity award.

Type of Ironwood Award	Our Employees	Ironwood Employees
Vested Stock Options (other than Vested Incentive Stock Options granted under the Ironwood 2010 Incentive Plan)	Continue to hold vested Ironwood stock options and receive a pro rata portion of our vested stock options, each as equitably adjusted to reflect the distribution	Continue to hold vested Ironwood stock options and receive a pro rata portion of our vested stock options, each as equitably adjusted to reflect the distribution
Vested Incentive Stock Options (ISOs) granted under the Ironwood 2010 Incentive Plan	Substitute with our vested ISOs, unless employee elects to convert to non-qualified stock options of both us and Ironwood, each as equitably adjusted to reflect the distribution	Continue to hold vested Ironwood ISOs, unless employee elects to convert to non-qualified stock options of both us and Ironwood, each as equitably adjusted to reflect the distribution
Unvested Stock Options	Substitute with our unvested stock options of comparable value	Continue to hold unvested Ironwood stock options, as equitably adjusted to reflect the distribution
Restricted Stock Units (other than July 2018 Recognition Restricted Stock Units)	Substitute with our restricted stock units of comparable value	Continue to hold Ironwood restricted stock units, as equitably adjusted to reflect the distribution
July 2018 Recognition Restricted Stock Units	Continue to hold Ironwood restricted stock units, as equitably adjusted to reflect the distribution	Continue to hold Ironwood restricted stock units, as equitably adjusted to reflect the distribution

Each Ironwood equity award converted into an equity award issued by us is subject to substantially the same terms and vesting conditions as were applicable to the Ironwood equity awards prior to the distribution.

Private Placement

Common Stock Purchase Agreement

On February 25, 2019, we and various investors entered the purchase agreement pursuant to which these investors agreed to make an aggregate cash investment in us of up to $175.0 million in exchange for shares of our common stock at a purchase price per share determined as set forth below. The closing of the private placement occurred on April 2, 2019. At the closing of the private placement, we issued an aggregate of 11,817,165 shares of our common stock at a per share purchase price of $14.809, resulting in aggregate gross proceeds to us of $175.0 million.

The investors who participated in the private placement included the following, each of whom is either a director, an executive officer, an immediate family member of a director or executive officer, an entity related to such director, executive officer or immediate family member, or beneficially owns at least 5% of our common stock as of April 2, 2019, taking into account our shares of common stock issued in the private placement: accounts managed by direct or indirect subsidiaries of FMR LLC invested $17.0 million, MFN Partners, LP invested $15.0 million, American Endowment Foundation created, the entity that controls the donor advised fund by Dr. Hecht, invested $34.0 million, Dr. Currie

invested $4.0 million and Dr. Hecht's immediate family invested $6.8 million in the aggregate. Certain of these investors financed all or a portion of their investment in us through sales of Ironwood common stock.

The number of shares of our common stock issued to each investor at the closing of the private placement was determined by dividing the cash contribution made by each investor by $14.809, the purchase price, rounded up to the nearest whole share. The purchase price was determined by dividing $250.0 million, our pre-money valuation by 16,881,703, the number equal to the total number of (a) shares of our common stock outstanding, (b) our restricted stock units outstanding and (c) shares of our common stock issuable pursuant to the exercise of options outstanding (determined in accordance with the treasury stock method), in each case after giving effect to the distribution.

Covenants

Pursuant to the purchase agreement, we have various obligations after the closing, including, using commercially reasonable efforts to make all timely filings under the Exchange Act to enable investors to sell their shares under Rule 144, using commercially reasonable efforts to avoid any integration with any other offer or sale of securities that would require registration under the Securities Act, and timely filing a Form D and making all applicable securities and "Blue Sky" filings as may be required by federal and state securities laws.

Registration Rights

Pursuant to the terms of the purchase agreement, we were obligated within five business days after the closing of the private placement, to file this registration statement on Form S-1 with the SEC registering the resale of shares of our common stock held by the investors and to use commercially reasonable efforts to cause such registration statement to become effective. We also agreed to pay all expenses associated with the registration statement, except for underwriting discounts and commissions.

Pursuant to the terms of the purchase agreement, we will indemnify the investors for any damages arising out of or resulting from (a) any untrue or alleged untrue statement of a material fact contained in any registration statement under which shares of our common stock held by the investors are registered or sold or any other disclosure document produced by or on behalf of us or (b) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, provided that such indemnity will not apply to any damages arising out of or resulting from any untrue statement or omission contained in any information relating to such investor furnished in writing by an investor to us expressly for use in a registration statement, in which case, the investors will indemnify us for damages relating to such statements.

Related Party Transactions Policy

We have a related party transactions policy that governs the review and approval of related party transactions following the separation. Pursuant to this policy, if we want to enter into a transaction with a related party or an affiliate of a related party, our audit committee will review the proposed transaction to determine, based on applicable Nasdaq and SEC rules, whether such transaction is a related party transaction that requires pre-approval by our audit committee or our board of directors. If pre-approval is required, the proposed transaction will be reviewed at the next regular or special meeting of our audit committee or our board of directors, as applicable. We may not enter into a related party transaction unless our audit committee has specifically confirmed in writing that either no further reviews are necessary or that all requisite corporate reviews have been obtained.

Each of the agreements that we entered into with Ironwood or its subsidiaries, and any transactions contemplated thereby, are deemed to be approved and not subject to the terms of such policy.

PRINCIPAL AND SELLING STOCKHOLDERS

The following table sets forth information regarding beneficial ownership of our common stock as of April 2, 2019 held by:

- each person or group of affiliated persons we know to beneficially own 5% or more of the outstanding shares of our common stock;
- each of our named executive officers;
- each of our directors;
- all executive officers and directors as a group; and
- each selling stockholder.

We have determined beneficial ownership in accordance with the rules of the SEC and the information is not necessarily indicative of beneficial ownership for any other purpose. Unless otherwise indicated below, to our knowledge, the persons and entities named in the table have sole voting and sole investment power with respect to all shares that they beneficially own, subject to community property laws where applicable. In computing the number of shares of our common stock beneficially owned by a person and the percentage ownership of that person, we deemed outstanding shares of our common stock subject to options or restricted stock units held by that person that are currently exercisable, exercisable within 60 days of April 2, 2019 or vested and will settle within 60 days of April 2, 2019. We did not deem these shares outstanding, however, for the purpose of computing the percentage ownership of any other person. We have based our calculation of the percentage ownership of our common stock on 27,401,660 shares of our common stock outstanding as of April 2, 2019.

This table is based upon information supplied by officers, directors, selling stockholders and stockholders known by us to be beneficial owners of more than 5% of our common stock, information obtained from Schedules 13G or 13D filed with the SEC, and based on information publicly available reporting beneficial ownership of Ironwood common stock. Unless otherwise noted below, no selling stockholder has had any position, office or other material relationship with us or any of our predecessors or affiliates within the past three years. Unless otherwise indicated in the footnotes below, based on the information provided to us by or on behalf of the selling stockholders, no selling stockholder is a broker-dealer or an affiliate of a broker-dealer.

Unless otherwise indicated, the address of each beneficial owner listed on the table below is c/o Cyclerion Therapeutics, Inc. 301 Binney Street, Cambridge, MA 02142.

	Shares Beneficially Owned Prior to the Offering			Shares Beneficially Owned After the Offering(1)	
Name of Beneficial Owner	Number	Percentage (%)	Shares Being Offered	Number	Percentage (%)
Greater than 5% Stockholders:					
FMR LLC (Fidelity)(2)	2,668,952	9.7	1,181,716	1,487,236	5.4
American Endowment Foundation(3)	2,660,546	9.7	2,660,546	—	*
Wellington Management Group LLP(4)	1,960,006	7.2	—	1,960,006	7.2
MFN Partners, LP(5)	1,506,852	5.5	1,012,898	493,954	1.8
Named Executive Officers and Directors:					
Peter M. Hecht, Ph.D(6).	726,696	2.7	—	726,696	2.7
Mark G. Currie, Ph.D.(7)	515,240	1.9	270,107	245,133	*
William Huyett(8)	36,135	*	—	36,135	*
Kevin Churchwell	2,421	*	—	2,421	*
George Conrades	4,334	*	—	4,334	*
Marsha Fanucci	16,950	*	—	16,950	*
Ole Isacson	2,421	*	—	2,421	*
Stephanie Lovell	2,421	*	—	2,421	*
Terrance McGuire	18,120	*	—	18,120	*
Michael Mendelsohn	2,421	*	—	2,421	*
Amy Schulman	7,508	*	—	7,508	*
All directors and executive officers as a group(11 persons)	1,334,667	4.9	270,107	1,064,560	3.9
Selling Stockholders(9)				—	
Aberdare Management Company, LLC(10)	33,764	*	33,764	—	*
Amalie Kass 2008 CRUT	341,225	1.2	337,633	3,592	*
Anne Hecht	24,802	*	10,129	14,673	*
Artal International S.C.A.(11)	1,350,531	4.9	1,350,531	—	*
Baker Brothers Life Sciences, L.P.(12)	185,665	*	185,665	—	*
667, L.P.(12)	16,916	*	16,916	—	*
Brian M. Cali(13)	257,379	*	131,677	125,702	*
Bridger Healthcare Ltd(14)	1,262,266	4.6	844,082	418,184	1.5
Camber Capital Fund II(15)	4,525	*	4,525	—	*
Camber Capital Master Fund LP(15)	670,741	2.4	670,741	—	*
Christopher T. Walsh	40,218	*	16,882	23,336	*
CVI Investments, Inc.(16)	337,633	1.2	337,633	—	*
David E. Shaw Revocable Trust	337,633	1.2	337,633	—	*
David P. Schenkein 2004 Revocable Trust	6,753	*	6,753	—	*
D.S. Gregory 1987 Trust for Charlotte G. Surgenor(17)	20,768	*	16,882	3,886	*
EcoR1 Capital Fund Qualified, L.P.(18)	641,057	2.3	275,653	365,404	2.3
EcoR1 Capital Fund, L.P.(18)	135,149	*	61,981	73,168	*
Persons and Entities affiliated with Farallon Capital(19)	844,085	3.1	844,085	—	*
George Milne	33,764	*	33,764	—	*
G. Todd Milne and Jill C. Milne(20)	107,730	*	16,882	90,848	*
Joseph C. Cook, Jr.	40,914	*	33,764	7,150	*
Jonathan Hecht	33,953	*	16,882	17,071	*
Kenneth and Christina Hecht Living Trust	16,882	*	16,882	—	*
Martin J. Granoff	67,527	*	67,527	—	*
Miller Family Administrative Trust u/a DTD 10/16/02(21)	36,371	*	33,764	2,607	*
Monica Higgins	44,645	*	10,129	34,516	*
Pelmea Limited Partnership(22)	101,291	*	101,291	—	*
Point 72 Associates, LLC(23)	506,449	1.8	506,449	—	*
Robert Michael Hecht	50,007	*	27,011	22,996	*
Sean Tunis & Nancy Kass	33,147	*	23,635	9,512	*
The Charis Foundation, Inc.	36,764	*	33,764	3,000	*
Thomas David Hecht	41,201	*	16,882	24,319	*

(*) Less than 1%.

(1) Assumes the sale by the selling stockholders of all shares of common stock registered pursuant to the registration statement of which this prospectus forms a part.

(2) Based upon information provided to us and the information provided by FMR LLC ("FMR") and Abigail P. Johnson in a Schedule 13G/A filed on February 13, 2019, reporting ownership of Ironwood common stock as of December 31, 2018 and 1,181,716 shares issued in the private placement, the shares are held of record by accounts that are managed by direct or indirect subsidiaries of FMR LLC. Abigail P. Johnson is a Director, the Chairman, the Chief Executive Officer and the President of FMR LLC. Members of the Johnson family, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC

(3) Includes (i) 27,011 shares held by American Endowment Foundation re: Anne Hecht Donor Advised Fund, (ii) 2,295,902 shares held by American Endowment Foundation re: The Loon Fund and (iii) 337,633 shares held by American Endowment Foundation re: Alfred Moses Donor Advised Fund. The Address of the American Endowment Fund is 5700 Darrow Road, Ste. 118, Hudson, Ohio 44236.

(4) Based upon the information provided by Wellington Management Group LLP ("Wellington"), Wellington Group Holdings LLP ("Wellington Group"), Wellington Investment Advisors Holdings LLP ("Wellington Investment") and Wellington Management Company LLP ("Wellington Management," collectively with Wellington, Wellington Group and Wellington Investment, the "Wellington Entities") in a Schedule 13G/A filed on February 12, 2019, reporting ownership of Ironwood common stock as of December 31, 2018. According to the information included in this Schedule 13G/A, (i) each of Wellington, Wellington Group and Wellington Investment has sole voting and dispositive power with respect to none of these shares, shared voting power with respect to 1,183,989 of these shares, and shared dispositive power with respect to all of these shares and (ii) Wellington Management has sole voting and dispositive power with respect to none of these shares, shared voting power with respect to 1,144,593 of these shares, and shared dispositive power with respect to 1,807,923 of these shares. The address of the Wellington Entities is c/o Wellington Management Company LLP, 280 Congress Street, Boston, MA 02210.

(5) The general partner of MFN Partners, LP ("MFN Partnership") is MFN Partners GP, LLC ("MFN GP"). MFN Partners Management, LP ("MFN Management") acts as investment adviser to the MFN Partnership. The general partner of MFN Management is MFN Partners Management, LLC ("MFN LLC"). Farhad Nanji and Michael DeMichele are the managing members of MFN GP and MFN LLC, and collectively make voting and investment decisions with respect to shares held by the Partnership. The address of each of the foregoing is 222 Berkeley Street, 13th Floor, Boston, MA 02216.

(6) Includes 261,684 shares of common stock issuable to Dr. Hecht upon the exercise of options that are exercisable within 60 days following April 2, 2019.

(7) Includes 84,501 shares of common stock issuable to Dr. Currie upon the exercise of options that are exercisable within 60 days following April 2, 2019.

(8) Includes 34,729 shares of common stock issuable to Mr. Huyett upon the exercise of options that are exercisable within 60 days following April 2, 2019.

(9) The list of selling stockholders under the heading "Selling Stockholders" does not include selling stockholders listed under the headings "Greater than 5% Stockholders" and "Named Executive Officers and Directors".

(10) Paul Klingenstein is the managing member of Aberdare Management Company LLC ("Aberdare") and may be deemed to beneficially own all of the shares held by Aberdare.

(11) Artal International Management S.A. is the managing partner of Artal International S.C.A. Artal Group S.A. is the sole stockholder of Artal International Management S.A. Weslend S.A. is the sole stockholder of Artal Group S.A. Stichting Administratiekantoor Westend, or the Stichting, is the sole stockholder of Westend S.A. Pascal Minne is the sole member of the board of the Stichting. Accordingly, each of Artal International S.C.A., Artal International Management S.A., Artal Group S.A., Westend S.A., the Stichting and Pascal Minne may be deemed to beneficially own the shares of common stock held of record by Artal International S.C.A. The address of Artal International S.C.A., Artal International Management S.A., Artal Group S.A. and Westend S.A. is 44, Rue de Ia Vallee, L-2661, Luxembourg, Luxembourg. The address of the Stichting is Ijsselburcht 3, NL-6825 BS Arnhem, The Netherlands. The address of Pascal Minne is Rue de l'Industrie 44, B-1040, Bruxelles, Belgium.

(12) Baker Bros. Advisors LP (the "Adviser") is the investment adviser to each of 667, L.P. and Baker Brothers Life Sciences, L.P. (collectively, the "Baker Funds"). Baker Bros. Advisors (GP) LLC (the "Adviser GP") is the general partner of Adviser. Julian C. Baker and Felix J. Baker are managing members of Adviser GP. The Adviser has complete and unlimited discretion and authority with respect to the investment and voting power of the securities held by the Baker Funds, and may be deemed to have the power to vote or direct the vote of and the power to dispose or direct the disposition of such securities. Julian C. Baker and Felix J. Baker disclaim beneficial ownership of the securities held by the Baker Funds except to the extent of their pecuniary interest therein.

(13) Brian M. Cali serves as our SVP of Investor Relations and Corporate Communications. Includes (i) 143,666 shares of common stock, (ii) 102,361 shares of common stock issuable upon the exercise of options and (iii) 11,352 shares of common stock issuable upon the exercise of options that are exercisable within 60 days following April 2, 2019.

(14) Based on information provided by Bridger Healthcare Ltd., Bridger Management, LLC is the investment adviser to Bridger Healthcare, Ltd. Roberto Mignone is the Manager of Bridger Management, LLC and Blake Goodner is the Portfolio Manager of Bridger Healthcare, Ltd.

(15) Camber Capital Management, L.P. ("Camber Advisor") serves as the investment advisor to each of Camber Capital Fund II, L.P. and Camber Capital Master Fund L.P. Stephen DuBois serves as the Managing Member of Camber Advisor.

(16) Heights Capital Management, Inc. ("Heights") is the investment manager to CVI Investments, Inc. ("CVI") and may be deemed to be the beneficial owner of the shares held by CVI. Martin Kobinger, in his capacity as investment manager of Heights, may also be deemed to have investment discretion and voting power over the shares held by CVI.

(17) Charlotte G. Surgenor and The 1911 Trust Company are Trustees of the D.S. Gregory 1987 Trust for Charlotte G. Surgenor family. Kevin L. Kavanaugh is the President and Trustee of The 1911 Trust Company. In such capacities, each of Charlotte G. Surgenor and Mr. Kavanaugh may be deemed to have voting and dispositive powers over the shares held by the D.S. Gregory 1987 Trust for Charlotte G. Surgenor family. Mr. Kavanaugh disclaims beneficial ownership of these shares.

(18) Oleg Nodelman is the control person for EcoR1 Capital, LLC, the sole general partner of EcoR1 Capital Fund, L.P. and EcoR1 Capital Fund Qualified, L.P., and may be deemed to beneficially own the shares held of record by EcoR1 Capital Fund, L.P. and EcoR1 Capital Fund Qualified, L.P.

(19) Farallon Partners, L.L.C. is (i) the general partner of each of Farallon Capital Partners, L.P., Farallon Capital Institutional Partners, L.P., Farallon Capital Institutional Partners II, L.P., Farallon Capital Institutional Partners III, L.P., Farallon Capital Offshore Investors II, L.P. and Farallon Capital (AM) Investors, L.P. and (ii) the sole member of the Four Crossings Institutional Partners V, L.P.'s general partner, and may be deemed to be a beneficial owner of the 820,869 shares owned by the Farallon funds other than Farallon Capital F5 Masters I, L.P. Farallon Institutional (GP) V, L.L.C. is the general partner of Four Crossings Institutional Partners V, L.P. and may be deemed to be a beneficial owner of the 21,103 shares owned by Four Crossings Institutional Partners V, L.P. Farallon F5 (GP), L.L.C. is the general partner of Farallon Capital F5 Masters I, L.P. and may be deemed to be a beneficial owner of the 23,216 shares owned by Farallon Capital F5

Masters I, L.P. The following persons are each a managing member of Farallon Partners, L.L.C., a manager or senior manager, as the case may be, of Farallon Institutional (GP) V, L.L.C., and an authorized signatory of Farallon F5 (GP), L.L.C. and may be deemed to be a beneficial owner of all 844,085 shares owned by the Farallon Funds: Philip D. Dreyfuss, Michael B. Fisch, Richard B. Fried, David T. Kim, Monica R. Landry, Michael G. Linn, Rajiv A. Patel, Thomas G. Roberts, Jr., William Seybold, Andrew J. M. Spokes, John R. Warren and Mark C. Wehrly.

(20) G. Todd Milne serves as our VP of External Innovation and Corporate Development. Includes (i) 77,406 shares of common stock, (ii) 27,676 shares of common stock issuable upon the exercise of options and (iii) 2,648 shares of common stock issuable upon the exercise of options that are exercisable within 60 days following April 2, 2019.

(21) Based on information provided, in her capacity as the trustee of the Miller Family Administrative Trust u/a DTD 10/16/02 (the "GBM Trust"), Gina Bornino Miller may be deemed to have voting and dispositive powers over the shares held of record by the GBM Trust.

(22) Includes 33,764 shares held by Deep Blue Venture Partners and 67,527 shares held by Pelmea Limited Partnership. Based on information provided by Pelmea Limited Partnership, Norm Benford and William Wilson serve as managers of Pelmea LLC, GP, the general partner of Pelmea Limited Partnership, and may be deemed to beneficially own the shares held by Pelmea Limited Partnership.

(23) Point72 Asset Management maintains investment and voting power with respect to the securities held by certain investment funds it manages, including Point72 Associates LLC. Point72 Capital Advisors is the general partner of Point72 Asset Management. Mr. Steven A. Cohen controls each of Point72 Associates LLC and Point72 Asset Management and may be deemed to beneficially own the shares held of record by Point72 Associates LLC.

DESCRIPTION OF CAPITAL STOCK

General

The following description of our capital stock is intended as a summary only and is qualified in its entirety by reference to our articles of organization and bylaws, which have been filed as exhibits to the registration statement of which this prospectus is a part, and to the applicable provisions of the MBCA. The description of our capital stock reflects changes to our capital structure that occurred on April 1, 2019, upon the closing of this separation.

Our authorized capital stock consists of 400,000,000 shares of our common stock and 100,000,000 shares of our preferred stock, all of which preferred stock is undesignated. As of April 2, 2019, there were 27,401,660 shares of our common stock outstanding.

Common Stock

Dividend Rights

Subject to preferences that may apply to shares of preferred stock outstanding at the time, holders of outstanding shares of common stock are entitled to receive dividends out of assets legally available at the times and in the amounts as our board of directors may from time to time determine.

Voting Rights

Each outstanding share of common stock is entitled to one vote on all matters submitted to a vote of shareholders. Holders of shares of our common stock have no cumulative voting rights.

Preemptive Rights

Our common stock is not entitled to preemptive or other similar subscription rights to purchase any of our securities.

Conversion or Redemption Rights

Our common stock is neither convertible nor redeemable.

Liquidation Rights

Upon our liquidation, the holders of our common stock will be entitled to receive pro rata our assets which are legally available for distribution, after payment of all debts and other liabilities and subject to the prior rights of any holders of preferred stock then outstanding.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "CYCN."

Preferred Stock

Our board of directors may, without further action by our shareholders, from time to time, direct the issuance of shares of preferred stock in series and may, at the time of issuance, determine the designations, powers, preferences, privileges and relative participating, optional or special rights as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, voting rights, terms of redemption and liquidation preferences, any or all of which may be greater than the rights of the common stock. Satisfaction of any dividend preferences of outstanding shares of preferred stock would reduce the amount of funds available for the payment of dividends on shares of

our common stock. Holders of shares of preferred stock may be entitled to receive a preference payment in the event of our liquidation before any payment is made to the holders of shares of our common stock. Under certain circumstances, the issuance of shares of preferred stock may render more difficult or tend to discourage a merger, tender offer or proxy contest, the assumption of control by a holder of a large block of our securities or the removal of incumbent management. Upon the affirmative vote of a majority of the total number of directors then in office, our board of directors, without shareholder approval, may issue shares of preferred stock with voting and conversion rights which could adversely affect the holders of shares of our common stock and the market value of our common stock. There are currently no shares of preferred stock outstanding, and we have no present intention to issue any shares of preferred stock.

Anti-takeover Effects of Our Articles of Organization and Our Bylaws

Our articles of organization and bylaws contain certain provisions that are intended to enhance the likelihood of continuity and stability in the composition of our board of directors but which may have the effect of delaying, deferring or preventing a future takeover or change in control of us unless such takeover or change in control is approved by our board of directors.

These provisions include:

Action by written consent; special meetings of shareholders. Our articles of organization provide that shareholder action can be taken only at an annual or special meeting of shareholders or by the unanimous written consent of all shareholders in lieu of such a meeting. Our articles of organization and the bylaws also provide that, except as otherwise required by law, special meetings of the shareholders can only be called pursuant to a resolution adopted by a majority of our board of directors or holders of at least 40% of our then outstanding common stock. Except as described above, shareholders are not permitted to call a special meeting or to require our board of directors to call a special meeting.

Advance notice procedures. Our bylaws contain an advance notice procedure for shareholder proposals to be brought before an annual meeting of our shareholders, including proposed nominations of persons for election to the board of directors. Shareholders at an annual meeting will only be able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors or by a shareholder who was a shareholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has given our Secretary timely written notice, in proper form, of the shareholder's intention to bring that business before the meeting. Although our bylaws do not give our board of directors the power to approve or disapprove shareholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, the bylaws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of us.

Proxy Access. Our bylaws provide that a shareholder or a group of shareholders meeting certain conditions may nominate candidates for election as a director at an annual meeting of our shareholders using "proxy access" provisions. These provisions allow one or more shareholders (up to 20, collectively), owning at least 3% of our outstanding common stock continuously for at least three years, to nominate for election to our board of directors and to be included in our proxy materials up to the greater of two individuals or 20% of our board of directors, subject to the provisions included in our bylaws, including the provision of timely written notice to our Secretary.

Number of directors and filling vacancies; election of directors. Our articles of organization provide that the number of directors is established by the board of directors. Furthermore, any vacancy on our

board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office. The ability of our board of directors to increase the number of directors and fill any vacancies may make it more difficult for our shareholders to change the composition of our board of directors. Our bylaws provide that a majority of the votes properly cast for the election of a director shall effect such election unless there are more nominees than directorships, in which case a plurality standard shall apply.

Authorized but unissued shares. Our authorized but unissued shares of common stock and preferred stock are available for future issuance without shareholder approval. These additional shares may be utilized for a variety of corporate purposes, including future public offerings to raise additional capital, corporate acquisitions and employee benefit plans. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of a majority of our common stock by means of a proxy contest, tender offer, merger or otherwise.

Exclusive forum. Our articles of organization require, to the fullest extent permitted by law, that derivative actions brought in the name of Cyclerion, actions against our directors, officers and employees for breach of a fiduciary duty and other similar actions may be brought only in specified courts in the Commonwealth of Massachusetts. Although we believe this provision benefits us by providing increased consistency in the application of Massachusetts law in the types of lawsuits to which it applies, the provision may have the effect of discouraging lawsuits against our directors and officers. See "Risk Factors—Our articles of organization designate the state and federal courts located within the Commonwealth of Massachusetts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our shareholders, which could discourage lawsuits against us and our directors and officers."

Anti-Takeover Provisions under Massachusetts Law

Provisions Regarding Business Combinations

We are subject to the provisions of Chapter 110F of the MBCA. In general, Chapter 110F prohibits a publicly held Massachusetts corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An "interested stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, five percent or more of the corporation's voting stock.

Under Chapter 110F, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions: before the stockholder became interested, our board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder; upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 90% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or at or after the time the stockholder became interested, the business combination was approved by our board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

A Massachusetts corporation may "opt out" of these provisions with an express provision in its original articles of organization or an express provision in its articles of organization or bylaws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We

have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Provisions Regarding a Classified Board of Directors

Section 8.06(b) of the MBCA provides that, unless a company opts out of such provision, the terms of directors of a public Massachusetts company shall be staggered by dividing the directors into three groups, as nearly equal in number as possible, with only one group of directors being elected each year. We plan to opt out of this default requirement for a classified board of directors, and expect that all of our directors serve for one-year terms and will be elected annually.

Pursuant to Section 8.06(c)(2) of the MBCA, however, our board of directors may unilaterally opt back into default requirements under Section 8.06(b) of the MBCA and become a classified board of directors without the approval of our stockholders. Sections 8.06(d) and (e) of the MBCA provide that when a board of directors is so classified, (i) stockholders may remove directors only for cause, (ii) the number of directors shall be fixed only by the vote of the board of directors, (iii) vacancies and newly created directorships shall be filled solely by the affirmative vote of a majority of the remaining directors and (iv) a decrease in the number of directors will not shorten the term of any incumbent director. If our board of directors opts into this classified structure in the future, these provisions are likely to increase the time required for stockholders to change the composition of our board of directors. For example, at least two annual meetings would generally be necessary for stockholders to effect a change in a majority of the members of our board of directors. As a result, the ability of our board of directors to adopt a classified structure in the future without the approval of our stockholders could have the effect of discouraging a potential acquirer from making a tender offer for a majority of the outstanding voting interest of our capital stock or otherwise attempting to obtain control of Cyclerion.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

Indemnification of Directors and Officers

Our articles of organization provide that the liability of our directors for damages for any breach of fiduciary duty shall be limited to the fullest extent permitted by law. Our bylaws also provide that we will indemnify, and advance funds to and reimburse expenses of, our directors and officers that have been appointed by our board of directors to the fullest extent permitted by law, and that we may indemnify, and advance funds to and reimburse expenses of, such other officers and employees as determined by our board of directors. The right of indemnification provided under our bylaws is in addition to and not exclusive of any other rights to which any of our directors, officers or any other persons may otherwise be lawfully entitled. We have also entered, or expect to enter, into indemnification agreements with our directors and officers, and we carry insurance policies insuring our directors and officers against certain liabilities that they may incur in their capacity as directors and officers.

Part 8 of the MBCA authorizes the provisions, described above, that is contained in our articles of organization and bylaws. In addition, Sections 8.30 and 8.42 of the MBCA provide that if an officer or director discharges his or her duties in good faith and with the care that a person in a like position would reasonably exercise under similar circumstances and in a manner the officer or director reasonably believes to be in the best interests of the corporation, he or she will not be liable for such action.

SHARES ELIGIBLE FOR FUTURE SALE

Future sales of our common stock in the public market, or the availability of such shares for sale in the public market, could adversely affect market prices of our common stock prevailing from time to time. Sales of our common stock in the public market after such restrictions lapse, or the perception that those sales may occur, could adversely affect the prevailing market price at such time and our ability to raise equity capital in the future.

As of April 2, 2019 we had 27,401,660 shares of common stock issued and outstanding. All of the shares of our common stock sold pursuant to the registration statement of which this prospectus forms a part will be freely tradable without restriction or further registration under the Securities Act of 1933, as amended, or the Securities Act, unless such shares are purchased by our "affiliates" as that term is defined in Rule 144 under the Securities Act. As of the date of this prospectus, approximately 3.5% of our outstanding common stock is held by our affiliates. These shares will be "restricted securities" as that phrase is defined in Rule 144. Holders of restricted shares will be entitled to sell those shares in the public market if they qualify for an exemption from registration under Rule 144 or any other applicable exemption under the Securities Act. Subject to the provisions of Rules 144 and 701, additional shares will be available for sale as set forth below.

Rule 144

In general, under Rule 144 as currently in effect, a person who is not our affiliate and has not been our affiliate at any time during the preceding three months will be entitled to sell any shares of our common stock that such person has beneficially owned for at least six months, including the holding period of any prior owner other than one of our affiliates, without regard to volume limitations. Sales of our common stock by any such person are subject to the availability of current public information about us if the shares to be sold were beneficially owned by such person for less than one year.

In general, under Rule 144, as currently in effect, our affiliates or persons selling shares of our common stock on behalf of our affiliates are entitled to sell, within any three-month period, a number of shares that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal approximately 273,895 shares; or
- the average weekly trading volume of our common stock during the four calendar weeks preceding the filing of a notice on Form 144 with respect to such sale.

Sales under Rule 144 by our affiliates or persons selling shares on behalf of our affiliates are also subject to certain manner of sale provisions and notice requirements and to the availability of current public information about us.

Rule 701

Rule 701 generally allows a stockholder who purchased shares of our common stock pursuant to a written compensatory plan or contract and who is not deemed to have been an affiliate of our company during the immediately preceding 90 days to sell these shares in reliance upon Rule 144, but without being required to comply with the public information, holding period, volume limitation, or notice provisions of Rule 144. Rule 701 also permits affiliates of our company to sell their Rule 701 shares under Rule 144 without complying with the holding period requirements of Rule 144.

Registration Rights

As described in "Certain Relationships and Related Person Transactions—Relationship with Ironwood," we entered into the amended and restated common stock purchase agreement with certain investors. This prospectus is part of the registration statement filed pursuant to such amended and restated common stock purchase agreement. We do not have any other contractual obligations to register our common stock.

Registration Statement on Form S-8

We filed a registration statement on Form S-8 under the Securities Act to register shares of our capital stock subject to awards outstanding, as well as reserved for future issuance, under our equity compensation plans. The registration statement on Form S-8 became effective immediately upon filing, and shares of our common stock covered by the registration statement are eligible for sale in the public market, subject to the Rule 144 limitations applicable to affiliates, vesting restrictions, and any applicable market standoff agreements and lock-up agreements.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following is a discussion of the material U.S. federal income tax consequences of the acquisition, ownership, and disposition of our common stock to a non-U.S. holder that purchases shares of our common stock for cash in an amount equal to the stock's fair market value from a selling stockholder in a fully taxable transaction. For purposes of this discussion, a "non-U.S. holder" means a beneficial owner (other than a partnership or other pass-through entity) of our common stock that is not, for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation or any other organization taxable as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust if (i) the trust is subject to the primary supervision of a U.S. court and all substantial decisions of the trust are controlled by one or more U.S. persons or (ii) the trust has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

This discussion does not address the tax treatment of partnerships (or other entities that are treated as partnerships, grantor trusts, or other pass-through entities for U.S. federal income tax purposes) or persons that hold their common stock through partnerships, grantor trusts, or other pass-through entities. The tax treatment of a partner in a partnership or holder of an interest in another pass-through entity that will hold our common stock generally will depend upon the status of the partner or interest holder and the activities of the partner or interest holder and the partnership or other pass-through entity, as applicable. Such a partner or interest holder should consult his, her, or its own tax advisor regarding the tax consequences of the acquisition, ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

This discussion is based upon the provisions of the Internal Revenue Code of 1986, as amended, or the Code, the U.S. Treasury regulations promulgated thereunder, judicial decisions, and published rulings, administrative procedures, and other guidance of the Internal Revenue Service, or the IRS, all as in effect as of the date hereof. These authorities are subject to change and to differing interpretations, possibly with retroactive effect, which could result in U.S. federal income tax consequences different from those summarized below. No ruling has been or is expected to be sought from the IRS with respect to the matters summarized below, and there can be no assurance that the IRS will not take a contrary position regarding the U.S. federal income tax consequences of the acquisition, ownership, or disposition of our common stock, or that any such contrary position would not be sustained by a court.

This discussion is not a complete analysis of all of the potential U.S. federal income tax consequences relating to the acquisition, ownership, and disposition of our common stock by non-U.S. holders, nor does it address any U.S. federal estate, gift or generation-skipping transfer tax consequences, any tax consequences arising under any state, local, or non-U.S. tax laws, the impact of any applicable tax treaty, any consequences under the Medicare contribution tax on net investment income, the alternative minimum tax, or any consequences under other U.S. federal tax laws. In addition, this discussion does not address tax consequences resulting from a non-U.S. holder's particular circumstances or relating to non-U.S. holders that may be subject to special tax rules, including, without limitation:

- non-U.S. governments, agencies or instrumentalities thereof, or entities they control;
- "controlled foreign corporations" and their shareholders;

- "passive foreign investment companies" and their shareholders;
- partnerships, grantor trusts or other entities that are treated as pass-through entities for U.S. federal income tax purposes, and their owners;
- corporations that accumulate earnings to avoid U.S. federal income tax;
- former citizens or former long-term residents of the United States;
- banks, insurance companies or other financial institutions;
- tax-exempt pension funds or other tax-exempt organizations;
- persons who acquired our common stock pursuant to the exercise of employee stock options or otherwise as compensation;
- tax-qualified retirement plans;
- traders, brokers, or dealers in securities, commodities, or currencies;
- persons who hold our common stock as a position in a hedging transaction, wash sale, "straddle," "conversion transaction" or other risk reduction transaction or synthetic security;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes);
- persons who own or have owned, or are deemed to own or to have owned, more than 5% of our common stock (except to the extent specifically set forth below);
- persons deemed to sell our common stock under the constructive sale provisions of the Code; or
- persons subject to special tax accounting rules as a result of any item of gross income with respect to our common stock being taken into account in a financial statement.

Prospective investors should consult their own tax advisors regarding the particular U.S. federal income, estate, gift, and generation-skipping transfer tax consequences to them of acquiring, owning, and disposing of our common stock, as well as any tax consequences arising under any state, local, or foreign tax laws and any other U.S. federal tax laws. Prospective investors should also consult their tax advisors regarding the potential impact of any applicable income or estate tax treaty between the United States and such prospective investor's country of residence and of the rules described below under the heading "Foreign Account Tax Compliance Act."

Distributions on Common Stock

As described in the section entitled "Dividend Policy," we currently intend to retain all available funds and any future earnings, if any, and do not anticipate paying any cash dividends in the foreseeable future. The disclosure in this section addresses the consequences should our board of directors, in the future, determine to make a distribution of cash or property with respect to our common stock (other than certain distributions of stock which may be made free of tax), or to effect a redemption that is treated for tax purposes as a distribution. Any such distribution will generally constitute a dividend for U.S. federal tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent such a distribution exceeds both our current and our accumulated earnings and profits, such excess will be allocated ratably among the shares of common stock with respect to which the distribution is made. Any such excess allocated to a share of common stock will constitute a return of capital to the extent of the non-U.S. holder's adjusted tax basis in that share of common stock, reducing that adjusted tax basis, but not below zero. After the non-U.S. holder's adjusted tax basis in a share of common stock has been reduced to zero, any remaining excess allocated to that share of common stock will be treated

as capital gain from the sale of that share of common stock, subject to the tax treatment described below under "Gain on Disposition of Common Stock." Any such distributions will also be subject to the discussion below regarding backup withholding and foreign accounts. A non-U.S. holder's adjusted tax basis in a share of common stock is generally the purchase price of the share, reduced by the amount of any distributions constituting a return of capital with respect to that share.

Any dividend paid to a non-U.S. holder of our common stock generally will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividend, or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence. If a non-U.S. holder is eligible for benefits under an income tax treaty and wishes to claim a reduced rate of withholding, the non-U.S. holder generally will be required to provide us or our paying agent with a properly completed IRS Form W-8BEN, Form W-8BEN-E, or other applicable form, certifying under penalties of perjury the non-U.S. holder's qualification for the reduced rate. This certification must be provided to us or our paying agent prior to the payment of the dividend and may be required to be updated periodically. Special certification requirements apply to non-U.S. holders that hold common stock through certain foreign intermediaries. Non-U.S. holders that do not timely provide the required certifications, but that qualify for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. If we are not able to determine whether or not a distribution will exceed current and accumulated earnings and profits at the time the distribution is made, we may withhold tax on the entire amount of any distribution at the same rate as we would withhold on a dividend. However, a non-U.S. holder may obtain a refund of amounts that we withhold to the extent attributable to the portion of the distribution in excess of our current and accumulated earnings and profits.

If a non-U.S. holder holds our common stock in connection with the conduct of a trade or business in the U.S., and dividends paid on the common stock are effectively connected with the non-U.S. holder's U.S. trade or business (and, if required by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence, are attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the U.S., as defined under the applicable treaty), the non-U.S. holder will be exempt from U.S. federal withholding tax on the dividends. To claim the exemption, the non-U.S. holder must furnish a properly executed IRS Form W-8ECI (or other applicable form) prior to the payment of the dividends. Any dividends paid on our common stock that are effectively connected with a non-U.S. holder's U.S. trade or business (and satisfy any other applicable treaty requirements) generally will be subject to U.S. federal income tax on a net income basis at the regular graduated U.S. federal income tax rates generally applicable to U.S. persons (as defined in the Code). A non-U.S. holder that is treated as a corporation for U.S. federal income tax purposes also may be subject to an additional branch profits tax equal to 30% (or such lower rate as is specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence) of a portion of its earnings and profits for the taxable year that are effectively connected with a U.S. trade or business, as adjusted for certain items.

Gain on Disposition of Common Stock

Subject to the discussion below regarding backup withholding and foreign accounts, a non-U.S. holder generally will not be subject to U.S. federal income tax on any gain realized upon the sale, exchange, or other taxable disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a U.S. trade or business (and, if required by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the U.S.), in which case the non-U.S. holder will generally be required to pay tax on the gain derived from the sale, exchange, or other taxable disposition (net of certain deductions or credits) under regular graduated U.S. federal

income tax rates generally applicable to U.S. persons, and in the case of a non-U.S. holder that is treated as a corporation for U.S. federal income tax purposes, such non-U.S. holder may be subject to a branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence;

- the non-U.S. holder is an individual who is present in the U.S. for a period or periods aggregating 183 days or more during the taxable year in which the sale, exchange, or other taxable disposition occurs and certain other conditions are met, in which case the non-U.S. holder will be subject to U.S. federal income tax at a flat 30% rate (or such lower rate as is specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence) on the net gain derived from the sale, exchange, or other taxable disposition, which gain may be offset by U.S. source capital losses (even though the non-U.S. holder is not considered a resident of the U.S.) provided that the non-U.S. holder has timely filed U.S. federal income tax returns reporting those losses; or

- our common stock is a "United States real property interest" by reason of our status as a "United States real property holding corporation," or USRPHC, for U.S. federal income tax purposes during the five-year period preceding such sale, exchange or other taxable disposition (or the non-U.S. holder's holding period, if shorter).

Generally, a corporation is a USRPHC only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. We believe we are not now and we do not anticipate becoming a USRPHC. However, there can be no assurance that we are not now a USRPHC or will not become one in the future. Even if we are or become a USRPHC, for so long as our common stock is "regularly traded," as defined by applicable U.S. Treasury regulations, on an established securities market, sales of our common stock generally will not be subject to tax for non-U.S. holders that have not held more than 5% of our common stock, actually or constructively, during the five-year period preceding such non-U.S. holder's sale, exchange or other taxable disposition of our common stock (or the non-U.S. holder's holding period, if shorter). If we are determined to be a USRPHC and the foregoing exception does not apply, then the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to U.S. persons. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

Information Reporting and Backup Withholding

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect to dividends on our common stock. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above in "Distributions on Common Stock," generally will be exempt from U.S. backup withholding.

Information reporting and backup withholding will generally apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with

substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker.

Non-U.S. holders should consult their tax advisors regarding the application of the information reporting and backup withholding rules to them. Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement. Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder's U.S. federal income tax liability, if any, provided that an appropriate claim is filed with the IRS in a timely manner.

Foreign Account Tax Compliance Act

Sections 1471 to 1474 of the Code (commonly referred to as the Foreign Account Tax Compliance Act, or FATCA) generally impose withholding tax on certain types of payments made to "foreign financial institutions" (as defined in the Code) and other non-U.S. entities unless those institutions and entities meet additional certification, information reporting and other requirements. FATCA generally imposes a 30% withholding tax on dividends on our common stock paid to a foreign financial institution unless the foreign financial institution enters into an agreement with the U.S. Treasury to, among other things, (i) undertake to identify accounts held by certain U.S. persons (including certain equity and debt holders of such institution) or by U.S.-owned foreign entities, (ii) annually report certain information about such accounts, and (iii) withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. In addition, subject to certain exceptions, FATCA imposes a 30% withholding tax on the same types of payments to a "non-financial foreign entity" (as defined in the Code) unless the entity certifies that it does not have any substantial U.S. owners (which generally include any U.S. persons who directly or indirectly own more than 10% of the entity) or furnishes identifying information regarding each such substantial U.S. owner or agrees to report that information to the IRS. Withholding under FATCA generally will not be reduced or limited by bilateral income tax treaties. However, intergovernmental agreements between the U.S. and other countries with respect to the implementation of FATCA and non-U.S. laws, regulations and other authorities enacted or issued with respect to those intergovernmental agreements may modify the FATCA requirements described above. Non-U.S. holders should consult their own tax advisors regarding the possible implications of FATCA on their investment in our common stock and the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

PLAN OF DISTRIBUTION

We are registering the shares covered by this prospectus to permit the selling stockholders to conduct public or private secondary trading of these shares from time to time after the date of this prospectus. We will not receive any of the proceeds from the sale of the shares covered by this prospectus. The aggregate proceeds to the selling stockholders from the sale of the shares will be the purchase price of the shares less any discounts and commissions.

We will not pay any brokers' discounts and commissions in connection with the registration and sale of the shares covered by this prospectus by the selling stockholders. The selling stockholders reserve the right to accept and, together with their respective agents, to reject, any proposed purchases of the shares to be made directly or through agents.

The shares covered by this prospectus may be sold from time to time to purchasers directly by the selling stockholders. We will make copies of this prospectus available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act and pursuant to the purchase agreement.

- the shares may be sold in one or more transactions at:
- fixed prices;
- prevailing market prices at the time of sale;
- prices related to such prevailing market prices;
- varying prices determined at the time of sale; or
- negotiated prices.

These sales may be effected in one or more transactions:

- on any national securities exchange or quotation service on which the shares may be listed or quoted at the time of sale, including Nasdaq;
- in the over-the-counter market;
- in transactions otherwise than on such exchanges or services or in the over-the-counter market;
- in ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- in an exchange distribution in accordance with the rules of the applicable exchange;
- in privately negotiated transactions;
- in settlement of short sales, to the extent permitted by law;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange of otherwise;
- through any other method permitted by applicable law; or
- through any combination of the foregoing.

These transactions may include block transactions or crosses. Crosses are transactions in which the same broker acts as an agent on both sides of the trade.

In connection with the sales of the shares or otherwise, the selling stockholders may enter into hedging transactions with broker-dealers, which may in turn engage in short sales of the shares in the course of hedging in positions they assume. The selling stockholders may also sell the shares short and deliver the shares covered by this prospectus to close out short positions and to return borrowed shares

in connection with such short sales. The selling stockholders may also enter into option or other transactions with broker-dealers, who may then resell or otherwise transfer those shares. The selling stockholders may also loan or pledge the shares to broker-dealers that in turn may sell such shares. The selling stockholders may also transfer the shares in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus and may sell the shares from time to time under this prospectus after we have filed a supplement to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act supplementing or amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus. We may suspend the sale of shares by the selling stockholders pursuant to this prospectus for certain periods of time for certain reasons, including if the prospectus is required to be supplemented or amended to include additional material information.

We know of no existing arrangements between any selling stockholder, any other stockholder, broker, dealer, underwriter, or agent relating to the sale of the shares offered by this prospectus. The selling stockholders will act independently of us in making decisions with respect to the timing, manner, and size of each resale or other transfer. There can be no assurance that the selling stockholders will sell any or all of the shares under this prospectus. Further, we cannot assure you that the selling stockholders will not transfer, distribute, devise or gift the shares by other means not described in this prospectus. In addition, any shares covered by this prospectus that qualify for sale under Rule 144 of the Securities Act may be sold under Rule 144 rather than under this prospectus. The shares may be sold in some states only through registered or licensed brokers or dealers. In addition, in some states the shares may not be sold unless they have been registered or qualified for sale or an exemption from registration or qualification is available and complied with.

The selling stockholders and any broker-dealers or agents that are involved in selling the shares may be deemed to be "underwriters" within the meaning of the Securities Act in connection with such sales. In such event, any commissions received by such broker-dealers or agents and any profit on the resale of the shares purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act.

The selling stockholders and any other person participating in the sale of the shares will be subject to the Exchange Act. The Exchange Act rules include, without limitation, Regulation M, which may limit the timing of purchases and sales of any of the shares by the selling stockholders and any other person. In addition, Regulation M may restrict the ability of any person engaged in the distribution of the shares to engage in market-making activities with respect to the particular shares being distributed. This may affect the marketability of the shares and the ability of any person or entity to engage in market-making activities with respect to the shares.

With respect to those shares being registered pursuant to the purchase agreement, we have agreed to indemnify or provide contribution to the selling stockholders and all of their officers, directors and control persons, as applicable. The selling stockholders have agreed to indemnify us in certain circumstances against certain liabilities, including certain liabilities under the Securities Act. We agreed to cause the registration statement of which this prospectus is a part to remain effective for the period set forth in the purchase agreement. Once sold under the registration statement of which this prospectus forms a part, the shares will be freely tradeable in the hands of persons other than our affiliates.

LEGAL MATTERS

The validity of the shares of our common stock registered hereunder will be passed upon for us by Morgan, Lewis & Bockius LLP, Boston, Massachusetts.

EXPERTS

The combined financial statements of Cyclerion Therapeutics, Inc. as of December 31, 2018 and 2017, and for each of the two years in the period ended December 31, 2018, appearing in this prospectus and registration statement have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon appearing elsewhere herein, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 under the Securities Act of which this prospectus forms a part with respect to the sale of the shares by the selling stockholders. This prospectus is part of, and does not contain all of the information set forth in, the registration statement and the exhibits thereto. Some items are omitted in accordance with the rules and regulations of the SEC. For further information with respect to us and our common stock, we refer you to the registration statement and the exhibits filed therewith. Statements contained in this prospectus as to the contents of any contract, agreement or any other document referred to are summaries of the material terms of the respective contract, agreement or other document. With respect to each of these contracts, agreements or other documents filed as an exhibit to the registration statement, reference is made to the exhibits for a more complete description of the matter involved.

A copy of the registration statement, and the exhibits thereto, may be accessed without charge through the SEC's electronic data gathering, analysis and retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (www.sec.gov). Our website is www.cyclerion.com. The information that will be contained on, or that will be accessible through, our website is not a part of this prospectus, and you should not consider any information on, or accessible through, our website as part of this prospectus. We have included our website address in this registration statement solely as an inactive textual reference.

We are subject to the information and periodic reporting requirements of the Exchange Act and, accordingly, file annual reports containing financial statements audited by an independent public accounting company, quarterly reports containing unaudited financial statements, current reports, proxy statements and other information with the SEC. You are also able to access these materials without charge at the SEC's website. You are also able to access, free of charge, our reports filed with the SEC (for example, our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K and any amendments to those forms) through our website. Reports filed with or furnished to the SEC will be available as soon as reasonably practicable after they are filed with or furnished to the SEC.

INCORPORATION BY REFERENCE

As a "smaller reporting company", the SEC allows us to "incorporate by reference" certain of the information that we file with it after the date of the filing of the registration statement of which this prospectus forms a part, which means that we can disclose important information to you by referring you to documents containing that information. The information incorporated by reference is considered to be part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We hereby incorporate by reference any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than information determined to be furnished and not filed with the SEC), after the date of the initial filing of the registration statement of which this prospectus forms a part and prior to the effectiveness of such registration statement, and until the termination of the offering described in this prospectus. Any statement contained herein, or in any documents incorporated or deemed to be incorporated by reference herein, shall be deemed to be modified or superseded for the purpose of this prospectus to the extent that a subsequent statement contained herein or in any subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Cyclerion Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying combined balance sheets of Cyclerion Therapeutics, Inc. (the Company) as of December 31, 2018 and 2017, and the related combined statements of operations, net parent investment and cash flows for each of the two years in the period ended December 31, 2018, and the related notes (collectively referred to as the "combined financial statements"). In our opinion, the combined financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Emphasis of matter

Since the date of completion of our audit of the accompanying combined financial statements and initial issuance of our report thereon dated March 4, 2019, which report contained other matter paragraph regarding the Company's ability to continue as a going concern, the Company, as discussed in Note 11, has completed an issuance of its common stock for gross proceeds of $175.0 million (net proceeds of $165.0 million). Therefore, the conditions that raised substantial doubt about whether the Company will continue as a going concern no longer exist.

/s/ Ernst & Young LLP
We have served as the Company's auditor since 2018.
Boston, Massachusetts
March 4, 2019
except for Note 11, as to which the date is
April 9, 2019

Cyclerion Therapeutics, Inc.

Combined Balance Sheets

(In thousands)

	December 31, 2017	December 31, 2018
ASSETS		
Current assets:		
Prepaid expenses	$ 1,251	$ 867
Other current assets	8	12
Total current assets	1,259	879
Property and equipment, net	4,131	6,497
Other assets	80	25
Total assets	$ 5,470	$ 7,401
LIABILITIES AND NET PARENT INVESTMENT		
Current liabilities:		
Accounts payable	$ 1,802	$ 2,781
Accrued research and development costs	4,905	5,261
Accrued expenses and other current liabilities	7,330	9,804
Total current liabilities	14,037	17,846
Net parent investment:		
Net parent investment	(8,567)	(10,445)
Total liabilities and net parent investment	$ 5,470	$ 7,401

The accompanying notes are an integral part of these combined financial statements.

Cyclerion Therapeutics, Inc.

Combined Statements of Operations

(In thousands)

	Years Ended December 31,	
	2017	2018
Cost and expenses:		
Research and development	$ 78,803	$ 87,716
General and administrative	15,119	27,536
Total cost and expenses	93,922	115,252
Loss from operations	(93,922)	(115,252)
Net loss	$ (93,922)	$ (115,252)

The accompanying notes are an integral part of these combined financial statements.

Cyclerion Therapeutics, Inc.

Combined Statements of Net Parent Investment

(In thousands)

	Parent Company Net Investment
Ending Parent company net investment as of December 31, 2016	$ (6,761)
Net loss	(93,922)
Net transfers from Parent	82,622
Parent allocation—Share-based compensation	9,494
Ending Parent company net investment as of December 31, 2017	(8,567)
Net loss	(115,252)
Net transfer from Parent	100,941
Parent allocation—Share-based compensation	12,433
Ending Parent company net investment as of December 31, 2018	$ (10,445)

The accompanying notes are an integral part of these combined financial statements.

Cyclerion Therapeutics, Inc.

Combined Statements of Cash Flows

(In thousands)

	Year Ended December 31,	
	2017	2018
Cash flows from operating activities:		
Net loss	$ (93,922)	$ (115,252)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	1,745	1,528
Share-based compensation expense	9,494	12,433
Changes in assets and liabilities:		
Prepaid expenses	(1,034)	384
Other current assets	50	(4)
Other assets	(80)	55
Accounts payable	392	979
Accrued research and development costs	2,692	356
Accrued expenses and other current liabilities	(555)	2,018
Net cash used in operating activities	(81,218)	(97,503)
Cash flows from investing activities:		
Purchases of property and equipment	(1,404)	(3,438)
Net cash used in investing activities	(1,404)	(3,438)
Cash flows from financing activities:		
Transfer from Parent Company	82,622	100,941
Net cash provided by financing activities	82,622	100,941
Net increase (decrease) in cash and cash equivalents	—	—
Cash and cash equivalents, beginning of period	$ —	$ —
Cash and cash equivalents, end of period	$ —	$ —
Supplemental cash flow disclosure:		
Non-cash investing activities		
Fixed asset purchases in accounts payable and accrued expenses	$ 872	$ 455

The accompanying notes are an integral part of these combined financial statements.

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements

1. Nature of Business

Nature of Operations

Cyclerion Therapeutics, Inc. ("Cyclerion" or the "Company") is a clinical-stage biopharmaceutical company harnessing the power of soluble guanylate cyclase ("sGC") pharmacology to discover, develop and commercialize breakthrough treatments for serious and orphan diseases. Cyclerion's focus is enabling the full therapeutic potential of next-generation sGC stimulators. The Company's strategy rests on a solid scientific foundation that is enabled by our people and capabilities, external collaborations, and a responsive capital allocation approach.

The Separation

In May 2018, Ironwood Pharmaceuticals, Inc. ("Ironwood" or the "Parent") announced its plans to separate its sGC business from its commercial and gastrointestinal business through a pro rata distribution of Cyclerion's common stock to stockholders of Ironwood. As a part of the separation, Ironwood intends to transfer the assets, liabilities and operations of its sGC stimulator and discovery research business to Cyclerion, pursuant to the terms of a separation agreement, to be entered into between Ironwood and Cyclerion. On the distribution date, each Ironwood stockholder will receive one share of Cyclerion's common stock for every 10 shares of Ironwood common stock held at the close of business on the record date for the distribution. Registered stockholders will receive cash in lieu of any fractional shares of Cyclerion's common stock that they would have received as a result of the application of the distribution ratio. Following the distribution, Cyclerion will operate as a separate, independent, publicly traded company. The separation is expected to be completed in the first half of 2019, subject to customary market, regulatory, and other considerations. The separation is anticipated to be tax-free to Ironwood stockholders. Accordingly, after the anticipated tax-free separation all of the related tax attributes of Ironwood will remain with Ironwood.

Basis of Presentation

The accompanying combined financial statements have been prepared on a stand-alone basis and are derived from Ironwood's consolidated financial statements and accounting records. The combined financial statements reflect the historical results of the operations, financial position and cash flows of Cyclerion, in conformity with United States generally accepted accounting principles ("U.S. GAAP").

These combined financial statements of Cyclerion reflect the assets, liabilities, and expenses directly attributable to Cyclerion, as well as allocations of certain corporate level assets, liabilities and expenses, deemed necessary to fairly present the financial position, results of operations and cash flows of Cyclerion, as discussed further below. As such, these allocations may not be indicative of the actual amounts that would have been recorded had Cyclerion operated as an independent, publicly traded company for the periods presented.

As part of Ironwood, Cyclerion was dependent upon Ironwood for all of its working capital and financing requirements, as Ironwood uses a centralized approach to cash management and financing its operations. There were no cash amounts specifically attributable to Cyclerion for the historical periods presented; therefore, there is no cash reflected in the combined financial statements. Accordingly, cash and cash equivalents, debt or related interest expense have not been allocated to Cyclerion in the combined financial statements. Financing transactions related to Cyclerion are accounted for as a component of Net Parent Investment in the combined balance sheets and as a financing activity on the

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

1. Nature of Business (Continued)

accompanying combined statements of cash flows. Cyclerion's combined financial statements include an allocation of expenses related to certain Ironwood corporate functions, including senior management, legal, human resources, finance, information technology and quality assurance. These expenses have been allocated to Cyclerion based on direct usage or benefit where identifiable, with the remainder allocated pro-rata based on project related costs, headcount or other measures. These allocations may not be indicative of the actual expense that would have been incurred had Cyclerion operated as an independent, publicly traded company for the periods presented. See Notes 9 and 11 for further description of the accounting for the separation from Ironwood. The combined balance sheets of Cyclerion include assets and liabilities that were allocated principally on a specific identification basis. As Cyclerion was not historically held by a single legal entity, Net Parent Investment is shown in lieu of stockholder's equity in the combined financial statements. Net Parent Investment represents the cumulative investment by Ironwood in Cyclerion through the dates presented, inclusive of operating results. Balances between Cyclerion and Ironwood that were not historically settled in cash are included in Net Parent Investment. All significant transactions between the Company and Ironwood have been included in the accompanying combined financial statements. Transactions with Ironwood are reflected in the accompanying combined statements of Net Parent Investment as Net Transfers from Parent, and in the accompanying combined balance sheets within Net Parent Investment.

Going Concern

The Company has experienced negative operating cash flows for all historical periods presented. The Company expects these losses to continue into the foreseeable future as the Company continues the development and clinical testing of the product candidates, olinciguat, praliciguat and IW-6463, and its discovery research programs. The Company completed a private placement financing that would fund operations through at least the next 12 months (see Note 11), but has not received the cash associated with the financing as of the date these financial statements were available to be issued. Accordingly, the Company's continued operations are dependent on its ability to raise additional capital through the sale of equity or debt securities. In the event that the Company is unable to raise sufficient funds, it would have to substantially alter, or possibly even discontinue or curtail operations, or sell assets at distressed prices. This uncertainty raises substantial doubt about the Company's ability to continue as a going concern as of December 31, 2018. The accompanying financial statements do not include any adjustments that might result from the outcome of this uncertainty. The Company has entered into a common stock purchase agreement, pursuant to which, upon the completion of the distribution, the Company will receive cash in exchange for shares of Cyclerion common stock (see Note 11).

2. Summary of Significant Accounting Policies

Principles of Combination

The accompanying combined financial statements include the accounts of Cyclerion. All significant intercompany transactions with Ironwood are deemed to have been paid in the period the costs were incurred. Expenses related to corporate allocations from Ironwood to the Company are considered to be effectively settled for cash in the combined financial statements at the time the transaction was recorded.

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

Segment Information

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by the Company's chief operating decision-maker in deciding how to allocate resources and in assessing performance. The Company currently operates in one reportable business segment—human therapeutics.

Use of Estimates

The preparation of combined financial statements in accordance with U.S. GAAP requires the Company's management to make estimates and judgments that may affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the combined financial statements, and the amounts of expenses during the reported periods. On an on-going basis, the Company's management evaluates its estimates, judgments and methodologies. Significant estimates and assumptions in the combined financial statements include those related to allocations of expenses, assets and liabilities from Ironwood's historical financials to the Company; impairment of long-lived assets; income taxes, including the valuation allowance for deferred tax assets; research and development expenses; contingencies and share-based compensation. The Company bases its estimates on historical experience and on various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results may differ materially from these estimates under different assumptions or conditions. Changes in estimates are reflected in reported results in the period in which they become known.

Cash and Cash Equivalents

The Company considers all highly liquid investment instruments with a remaining maturity when purchased of three months or less to be cash equivalents. Investments qualifying as cash equivalents may consist of money market funds, U.S. government-sponsored securities and repurchase agreements. The carrying amount of cash equivalents approximates fair value. There were no cash amounts specifically attributable to Cyclerion for the historical periods presented; therefore, there is no cash reflected in the combined financial statements.

Property and Equipment

Property and equipment are recorded at cost, and are depreciated when placed into service using the straight-line method based on their estimated useful lives as follows:

Asset Description	Estimated Useful Life (In Years)
Laboratory equipment	5
Computer and office equipment	3
Furniture and fixtures	7
Software	3

Included in property and equipment are certain costs of software obtained for internal use. Costs incurred during the preliminary project stage are expensed as incurred, while costs incurred during the application development stage are capitalized and amortized over the estimated useful life of the

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

software. The Company also capitalizes costs related to specific upgrades and enhancements when it is probable the expenditures will result in additional functionality. Maintenance and training costs related to software obtained for internal use are expensed as incurred. Costs for capital assets not yet placed into service have been capitalized as construction in progress, and are depreciated in accordance with the above guidelines once placed into service. Maintenance and repair costs are expensed as incurred.

Impairment of Long-Lived Assets

The Company regularly reviews the carrying amount of its long-lived assets to determine whether indicators of impairment may exist, which warrant adjustments to carrying values or estimated useful lives. If indications of impairment exist, projected future undiscounted cash flows associated with the asset are compared to the carrying amount to determine whether the asset's value is recoverable. If the carrying value of the asset exceeds such projected undiscounted cash flows, the asset will be written down to its estimated fair value. There were no significant impairments of long-lived assets for the years ended December 31, 2017 and 2018.

Income Taxes

Income taxes as presented herein include current and deferred income taxes of Ironwood allocated to the Company's standalone financial statements in a manner that is systematic, rational and consistent with the asset and liability method prescribed by the Accounting Standards Codification ("ASC") Topic 740, *Income Taxes* ("Topic 740"). Accordingly, the Company's income tax provision was prepared following the "Separate Return Method." The Separate Return Method applies Topic 740 to the standalone financial statements of each member of the consolidated group as if the group member were a separate taxpayer and a standalone enterprise. As a result, actual tax transactions included in the consolidated financial statements of Ironwood may not be included in the combined financial statements of Cyclerion. Similarly, the tax treatment of certain items reflected in the combined financial statements of Cyclerion may not be reflected in the consolidated financial statements and tax returns of Ironwood; therefore, items such as net operating losses, credit carryforwards and valuation allowances may exist in the standalone financial statements that may or may not exist in the Parent's consolidated financial statements.

Cyclerion provides for income taxes under the asset and liability method. Deferred tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates in effect when the differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance to reflect the uncertainty associated with their ultimate realization.

Cyclerion accounts for uncertain tax positions recognized in the combined financial statements in accordance with the provisions of Topic 740 by prescribing a more-likely-than-not threshold for financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. When uncertain tax positions exist, Cyclerion recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. Cyclerion evaluates uncertain tax positions on a quarterly basis and adjusts the level of the liability to reflect any subsequent changes in the relevant facts surrounding the uncertain positions. Any changes to these estimates, based on the

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

actual results obtained and/or a change in assumptions, could affect Cyclerion's income tax provision in future periods. Interest and penalty charges, if any, related to unrecognized tax benefits would be classified as a provision for income tax in Cyclerion's combined statement of operations.

In general, the taxable loss of Cyclerion was included in Ironwood's U.S. consolidated and combined income tax returns, where applicable. As such, separate income tax returns were not prepared for Cyclerion. Consequently, income taxes currently payable are deemed to have been remitted to Ironwood in the period the liability arose and income taxes currently receivable are deemed to have been received from Ironwood in the period that a refund could have been recognized by Cyclerion had Cyclerion been a separate taxpayer, if applicable.

Research and Development Costs

The Company expenses research and development costs to operations as incurred. The Company defers and capitalizes nonrefundable advance payments made by the Company for research and development activities until the related goods are received or the related services are performed.

Research and development expenses are comprised of costs incurred in performing research and development activities, which may include salary, benefits and other employee-related expenses; share-based compensation expense; laboratory supplies and other direct expenses; facilities expenses; overhead expenses; third-party contractual costs relating to nonclinical studies and clinical trial activities and related contract manufacturing expenses, development of manufacturing processes and regulatory registration of third-party manufacturing facilities; licensing fees for the Company's product candidates; and other outside expenses.

General and Administrative Expenses

The Company expenses general and administrative costs to operations as incurred. General and administrative expense consists of compensation, share-based compensation, benefits and other employee-related expenses for personnel in the Company's administrative, finance, legal, information technology, business development and human resource functions. Other costs include the legal costs of pursuing patent protection of the Company's intellectual property, general and administrative related facility costs, insurance costs and professional fees for accounting and legal services.

Patent Costs

The Company incurred and recorded as operating expense legal and other fees related to patents of approximately $0.8 million and $0.9 million for the years ended December 31, 2017 and 2018, respectively. These costs were charged to general and administrative expenses as incurred.

Subsequent Events

The Company considers events or transactions that have occurred after the balance sheet date of December 31, 2018, but prior to the filing of the financial statements with the Securities and Exchange Commission to provide additional evidence relative to certain estimates or to identify matters that require additional recognition or disclosure. Subsequent events have been evaluated through the filing of the registration statement on Form S-1, of which this prospectus forms a part (see Note 11).

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

New Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board ("FASB") or other standard setting bodies that are adopted by the Company as of the specified effective date. Except as discussed elsewhere in the notes to the combined financial statements, the Company did not adopt any new accounting pronouncements during the years ended December 31, 2017 and 2018, that had a material effect on its combined financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* ("ASU 2016-02"), which supersedes the lease accounting requirements in ASC Topic 840, *Leases*, and most industry-specific guidance with ASC Topic 842, *Leases*. ASU 2016-02 requires the identification of arrangements that should be accounted for as leases by lessees. In general, for lease arrangements exceeding a 12-month term, these arrangements must now be recognized as assets and liabilities on the balance sheet of the lessee. Under ASU 2016-02, a right-of-use asset and lease obligation will be recorded for all leases, whether operating or financing, while the income statement will reflect lease expense for operating leases and amortization and interest expense for financing leases. The balance sheet amount recorded for existing leases at the date of adoption of ASU 2016-02 must be calculated using the applicable incremental borrowing rate at the date of adoption. ASU 2016-02 is effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted. In July 2018, the FASB issued ASU No. 2018-10, *Leases (Topic 842)* ("ASU 2018-10"), *Codification* Improvements and ASU No. 2018-11, *Leases (Topic 842)* ("ASU 2018-11"), to provide additional guidance for the adoption of Topic 842. ASU 2018-10 clarifies certain provisions, and corrects unintended applications of the guidance, such as the rate implicit in a lease, impairment of the net investment in a lease, lessee reassessment of lease classifications, lessor reassessment of lease term and purchase options, variable payments that depend on an index or rate and certain transition adjustments. The amendments in ASU 2018-11 will allow for an additional transition method, whereby at the adoption date the entity recognizes a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption, while the comparative period disclosures continue recognition under ASC Topic 840. Additionally, ASU 2018-11 includes a practical expedient for separating contract components for lessors. The Company's analysis includes, but is not limited to, reviewing existing leases, reviewing other service agreements for embedded leases, establishing policies and procedures, assessing potential disclosures and evaluating the impact of adoption on the Company's combined financial statements. The Company expects the adoption of ASU 2016-02, ASU 2018-10, and ASU 2018-11 to have a material impact on the Company's financial position and the related footnote disclosures.

In October 2016, the FASB issued ASU No. 2016-16, *Accounting for Income Taxes: Intra-Entity Asset Transfers of Assets Other than Inventory* ("ASU 2016-16"). ASU 2016-16 eliminates the ability to defer the tax expense related to intra-entity asset transfers other than inventory. Under the new standard, entities should recognize the income tax consequences on an intra-entity transfer of an asset other than inventory when the transfer occurs. ASU 2016-16 is effective for fiscal periods beginning after December 15, 2018. Early adoption is permitted. The Company continues to evaluate the potential impact that the adoption of ASU 2016-16 will have on the Company's financial position or results of operations. The Company does not expect the adoption of ASU 2016-16 to have a material impact on the Company's financial position or results of operations as of and for the year ended December 31, 2018.

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

2. Summary of Significant Accounting Policies (Continued)

In June 2018, the FASB issued ASU No. 2018-07, *Improvements to Nonemployee Share-based Payments ("ASU 2018-07")*. ASU 2018-07 simplifies the accounting for share-based payments to nonemployees by aligning with the accounting for share-based payments to employees, with certain exceptions. Measurement of equity-classified nonemployee awards issued in exchange for goods or services used or consumed in an entity's own operations will be fixed at the grant date, which may lower the cost and reduce volatility in the income statement. Entities also may use the expected term to measure nonemployee options or elect to use the contractual term as the expected term, on an award-by-award basis. ASU 2018-07 is effective for the fiscal periods beginning after December 15, 2018. The Company is currently evaluating the potential impact that the adoption of ASU 2018-07 may have on the Company's financial position and results of operations.

In August 2018, the FASB issued ASU No. 2018-15, *Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement that is a Service Contract* ("ASU 2018-15"). ASU 2018-15 requires a customer in a cloud computing arrangement that is a service contract to follow the internal-use software guidance in ASC 350-40, *Intangibles—Goodwill and Other—Internal Use Software* (ASC 350-40), to determine which implementation costs to capitalize as assets or expense as incurred. The internal-use software guidance in ASC 350-40 requires that certain costs incurred during the application development stage be capitalized and other costs incurred during the preliminary project and post-implementation stages be expensed as they are incurred. A customer's accounting for the hosting component of the arrangement is not affected by this guidance. The amendments in ASU 2018-15 are effective for fiscal years beginning after December 15, 2019, with early adoption permitted. The Company is currently evaluating the potential impact that the adoption of ASU 2018-15 may have on the Company's financial position and results of operations.

No other accounting standards known by the Company to be applicable to it that have been issued by the FASB or other standard-setting bodies and that do not require adoption until a future date are expected to have a material impact on the Company's combined financial statements upon adoption.

3. Property and Equipment

Property and equipment, net consisted of the following (in thousands):

	December 31,	
	2017	2018
Laboratory equipment	$ 17,088	$ 17,753
Software	2,732	2,593
Construction in progress	137	741
Computer and office equipment	35	901
Furniture and fixtures	8	—
Gross property and equipment	20,000	21,988
Less: accumulated depreciation and amortization	(15,869)	(15,491)
Property and equipment, net	$ 4,131	$ 6,497

As of December 31, 2017 and 2018, all of the Company's property and equipment was located in Cambridge, Massachusetts.

Depreciation and amortization expense of the Company's property and equipment was approximately $1.7 million and $1.5 million for the years ended December 31, 2017 and 2018, respectively.

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

4. Accrued Expenses and Other Liabilities

Accrued expenses consisted of the following (in thousands):

	December 31,	
	2017	2018
Accrued incentive compensation	$ 3,451	$ 4,889
Salaries	1,309	1,513
Accrued vacation	1,240	1,048
Professional fees	404	1,019
Workforce reduction charges	—	565
Other	926	770
	$ 7,330	$ 9,804

Other includes various accruals for goods received but not yet invoiced of approximately $0.5 million and $0.1 million for the years ended December 31, 2017 and 2018, respectively.

5. Commitment and Contingencies

Other Funding Commitments

As of December 31, 2017 and 2018, the Company has several on-going studies in various clinical trial stages. The Company's most significant clinical trial expenditures are related to contract research organizations. These contracts are generally cancellable, with notice, at the Company's option and do not have any significant cancellation penalties.

Guarantees

As permitted under Delaware law, Ironwood indemnifies its officers and directors for certain events or occurrences while the officer or director is, or was, serving at Ironwood's request in such capacity, including any such officers who serve as an officer or director of Cyclerion prior to the separation. The maximum potential amount of future payments Ironwood could be required to make is unlimited; however, Ironwood has directors' and officers' insurance coverage that is intended to limit its exposure and enable it to recover a portion of any future amounts paid. On September 6, 2018, Cyclerion was incorporated in Massachusetts, and is subject to Massachusetts law.

The Company enters into certain agreements with other parties in the ordinary course of business that contain indemnification provisions. These typically include agreements with directors and officers, business partners, contractors, clinical sites and customers. Under these provisions, the Company generally indemnifies and holds harmless the indemnified party for losses suffered or incurred by the indemnified party as a result of the Company's activities. These indemnification provisions generally survive termination of the underlying agreements. The maximum potential amount of future payments the Company could be required to make under these indemnification provisions is unlimited. However, to date the Company has not incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. As a result, the estimated fair value of these obligations is minimal. Accordingly, the Company did not have any liabilities recorded for these obligations as of December 31, 2017 and 2018.

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

6. Share-based Compensation Plans

Ironwood maintains certain share-based compensation programs for the benefit of its officers, directors and employees, including employees of Ironwood who will become employees of Cyclerion in connection with the separation. Specifically, during the years ended December 31, 2017 and 2018, Ironwood had two share-based compensation plans pursuant to which awards were made to employees of the Company: the Amended and Restated 2010 Employee, Director and Consultant Equity Incentive Plan ("2010 Equity Plan") and the Amended and Restated 2010 Employee Stock Purchase Plan ("2010 Purchase Plan"). Ironwood also had one share-based compensation plan under which there are outstanding awards available to employees of the Company, but from which no further awards will be made: the Amended and Restated 2005 Stock Incentive Plan ("2005 Equity Plan"). All awards granted under the programs consist of Ironwood shares of common stock. Accordingly, the amounts presented are not necessarily indicative of future share-based compensation and do not necessarily reflect the amount that Cyclerion would have issued as an independent, publicly traded company for the periods presented.

Share-based compensation expense was allocated to Cyclerion using a combined specific identification and pro-rata method based on internal project related costs and headcount that management believes are consistent and reasonable. Share-based compensation under Ironwood's incentive stock programs allocated to Cyclerion is reflected in the Company's combined statements of operations as follows for the years ended December 31, 2017 and 2018 (in thousands):

	Years Ended December 31,	
	2017	2018
Research and development	$ 6,068	$ 7,093
General and administrative	3,426	5,340
	$ 9,494	$ 12,433

Included in share-based compensation expense of approximately $9.5 million and $12.4 million, is approximately $2.2 million and $3.1 million of share-based compensation expense for employees that are directly attributable to Cyclerion for the years ended December 31, 2017 and 2018, respectively.

7. Income Taxes

The Company has historically operated as part of Ironwood and not as a stand-alone company. The combined financial statements have been derived from Ironwood's historical accounting records and are presented on a carve-out basis. The combined financial statements reflect Cyclerion's financial position, results of operations, and cash flows as if its business was operated as part of Ironwood prior to the separation, in conformity with U.S. GAAP. In general, Cyclerion has not recorded a provision for federal or state income taxes as it has had cumulative net operating losses since inception.

On December 22, 2017, the Tax Cuts and Jobs Act was enacted. This law substantially amended the Internal Revenue Code, including reducing the U.S. corporate income tax rates. Upon enactment, Cyclerion's deferred tax asset and related valuation allowance decreased by approximately $32.0 million. As the deferred tax asset is offset in full by the valuation allowance, this enacted legislation had no net impact on Cyclerion's financial position or results of operations. Cyclerion completed its accounting for

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

7. Income Taxes (Continued)

the tax effects of the Tax Cuts and Job Act as of December 31, 2018 and did not record any material adjustments to its original estimate.

A reconciliation of income taxes computed using the U.S. federal statutory rate to that reflected in operations follows (in thousands):

	Year Ended December 31,	
	2017	2018
Income tax benefit using U.S. federal statutory rate	$ (31,934)	$ (24,203)
State income taxes, net of federal benefit	(4,832)	(7,301)
Tax credits	(3,230)	(4,888)
Tax windfall	(26)	(106)
Effect of U.S. tax reform	32,057	—
Non-deductible share-based compensation	69	(111)
Permanent differences	9	40
Change in valuation allowance	7,887	36,569
	$ —	$ —

Components of the Company's deferred tax assets and liabilities are as follows (in thousands):

	Year Ended December 31,	
	2017	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 67,338	$ 97,049
Tax credit carryforwards	10,641	15,529
Capitalized research and development	5,121	6,169
Accruals and reserves	1,220	1,639
Share-based compensation	1,085	1,546
Total deferred tax assets	85,405	121,932
Deferred tax liabilities:		
Property and equipment	(576)	(556)
Total deferred tax liabilities	(576)	(556)
Net deferred tax assets	84,829	121,376
Valuation allowance	(84,829)	(121,376)
Net deferred tax assets	$ —	$ —

Management of Cyclerion has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Management has considered the Company's history of operating losses in addition to the expected timing of the reversal of existing temporary differences and concluded, in accordance with the applicable accounting standards, that it is more likely than not that the Company will not realize the benefit of its deferred tax assets. Accordingly, the net deferred tax

Cyclerion Therapeutics, Inc.

Notes to the Combined Financial Statements (Continued)

7. Income Taxes (Continued)

assets have been fully reserved at December 31, 2017 and 2018. Management reevaluates the positive and negative evidence on a quarterly basis.

The valuation allowance increased approximately by $7.9 million during the year ended December 31, 2017 primarily due to an increase in net operating losses and tax credit carryforwards, and partially offset by the decrease in net operating losses, tax credit carryforwards and other deferred tax assets as a result of the U.S. tax rate reduction resulting from tax reform.

The valuation allowance increased approximately by $36.6 million during the year ended December 31, 2018 primarily due to an increase in net operating losses and tax credit carryforwards.

At December 31, 2017 and 2018, Cyclerion has federal net operating loss carryforwards of approximately $246.7 million and $355.5 million, respectively, to offset future federal taxable income. Federal net operating losses generated prior to January 1, 2018 begin to expire in 2033 continuing through 2037 while federal net operating losses generated after January 1, 2018 will be carried indefinitely until utilized. As of December 31, 2017 and 2018, Cyclerion had state net operating loss carryforwards of approximately $245.8 million and $354.2 million, respectively, to offset future state taxable income, which will begin to expire in 2033 and will continue to expire through 2038. Cyclerion also had tax credit carryforwards of approximately $11.3 million and $16.5 million as of December 31, 2017 and 2018, respectively, to offset future federal and state income taxes, which expire beginning in 2033 and will continue to expire through 2038. These tax attributes reflect balances determined using the separate return method and do not represent actual amounts available for use. Note that Cyclerion will not generate net operating loss carryforwards or tax credit carryforwards available for its use until its inception and operation as a standalone legal entity.

Upon audit, taxing authorities may challenge all or part of an uncertain income tax position. While Cyclerion has no history of tax audits on a standalone basis, the Parent has been audited by federal and state taxing authorities in the past. Both Cyclerion and the Parent may be subject to tax audits by federal and state taxing authorities. Accordingly, the Parent and Cyclerion regularly assesses the outcome of potential examinations in each of the taxing jurisdictions when determining the adequacy of the amount of unrecognized tax benefit recorded. Cyclerion had no unrecognized tax benefits as of December 31, 2017 and 2018. Cyclerion will recognize interest and penalties, if any, related to uncertain tax positions in income tax expense. As of December 31, 2017 and 2018, no interest or penalties have been accrued.

The statute of limitations for assessment by the Internal Revenue Service ("IRS") and state tax authorities is open for tax years ended December 31, 2014, 2015, and 2016, although carryforward attributes that were generated prior to tax year 2014 may still be adjusted upon examination by the IRS or state tax authorities if they either have been, or will be, used in a future period. There are currently no federal or state income tax audits in progress.

8. Defined Contribution Plan

Ironwood maintains a defined contribution 401(k) Savings Plan in the form of a qualified 401(k) plan for the benefit of substantially all of its employees, which includes Ironwood employees who will become Cyclerion employees. Subject to certain IRS limits, eligible employees may elect to contribute from 1% to 100% of their compensation. Ironwood contributions to the plan are at the sole discretion of Ironwood's board of directors. Currently, Ironwood provides a matching contribution of

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Notes to the Combined Financial Statements (Continued)

8. Defined Contribution Plan (Continued)

75% of the employee's contributions, up to $6,000 annually. Compensation expense related to the 401(k) match was allocated to Cyclerion using a pro-rata method based on project related costs and headcount that management believes are consistent and reasonable. Included in compensation expense is approximately $0.3 million and $0.4 million of expenses for employees that are directly attributable to Cyclerion for the years ended December 31, 2017 and 2018, respectively.

9. Related Party Transactions

Relationship with Ironwood

Historically, the Company has been managed and operated in the normal course of business under Ironwood. Accordingly, certain shared costs have been allocated to the Company and reflected as expenses in the Company's stand-alone combined financial statements. The expenses reflected in the combined financial statements may not be indicative of expenses that will be incurred by the Company in the future.

(a) Corporate costs

Ironwood incurs significant corporate costs for services provided to Cyclerion. These costs include expenses for information systems, accounting, other financial services (such as treasury, audit and purchasing), human resources, legal, and facilities.

A portion of these costs benefit Cyclerion and are allocated to Cyclerion using a pro-rata method based on project related costs, headcount, or other measures that management believes are consistent and reasonable.

The allocated corporate costs included in the combined statement of operations were approximately $14.2 million and $18.3 million for the years ended December 31, 2017 and 2018, respectively, and were included in general and administrative expenses for both years.

(b) Cash Management and Financing

Cyclerion participates in Ironwood's centralized cash management and financing programs. Disbursements are made through centralized accounts payable systems which are operated by Ironwood. Cash receipts are transferred to centralized accounts, also maintained by Ironwood. As cash is disbursed and received by Ironwood, it is accounted for by Cyclerion through Net Parent Investment. All obligations are financed by Ironwood and financing decisions are determined by central Ironwood treasury operations.

Other Related Party Transactions

Ironwood has and currently obtains health insurance services for its employees, including employees of Ironwood who will become employees of Cyclerion, from an insurance provider whose President and Chief Executive Officer became a member of the Ironwood's Board of Directors in April 2016. Expenses related to insurance premiums were allocated to Cyclerion using a pro-rata method based on internal project assignments and headcount, that management believes are consistent and reasonable. Insurance premiums allocated to Cyclerion amounted to approximately $1.9 million and approximately $2.1 million, is reflected in the Company's combined statements of operations as follows for the years ended December 31, 2017 and 2018, and is reflected in the Company's combined statement of operations. Accordingly, the amounts presented are not necessarily indicative of future

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Notes to the Combined Financial Statements (Continued)

9. Related Party Transactions (Continued)

expense and do not necessarily reflect the results that Cyclerion would have experienced as an independent company for the periods presented. At December 31, 2017 and 2018, the Company had no outstanding payable balance due to this related party.

10. Workforce Reduction

On June 27, 2018, Ironwood, as part of its plans to separate its sGC business from its commercial and gastrointestinal business determined the initial organizational designs for the continuing Ironwood business and Cyclerion, including employees' roles and responsibilities. As part of this process Ironwood initiated, a reduction in its headquarter-based workforce by approximately 40 employees and substantially completed the reduction in its workforce during the year ending December 31, 2018. During the year ended December 31, 2018, Ironwood recorded approximately $5.2 million in total costs related to the reduction in workforce. Expense related to workforce reduction were allocated to Cyclerion using a pro-rata method based on internal project assignments and headcount, that management believes are consistent and reasonable. Workforce reduction charges allocated to Cyclerion amounted to approximately $2.0 million recorded in research and development expense and approximately $0.3 million recorded in general and administrative expense for the year ended December 31, 2018.

The following table summarizes the accrued liabilities activity recorded in connection with the reduction in workforce for the year ended December 31, 2018 (in thousands):

	Amounts Accrued at December 31, 2017	Charges	Amount Paid	Amounts Accrued at December 31, 2018
June 2018 Reduction	—	2,029	1,464	565
Total	—	$ 2,029	$ 1,464	$ 565

11. Subsequent Events

The Company has assessed subsequent events up through April 9, 2019, the date the financial statements were available to be issued.

On January 7, 2019, in connection with the distribution, the Company entered into a common stock purchase agreement, pursuant to which, upon the completion of the distribution, the Company will receive cash in exchange for shares of Cyclerion common stock.

On February 25, 2019, Cyclerion and various investors entered into an amended and restated common stock purchase agreement pursuant to which these investors agreed to make an aggregate cash investment in Cyclerion of up to $175.0 million in exchange for shares of Cyclerion common stock at a purchase price per share determined as set forth below.

On February 7, 2019, following further analysis of Ironwood's strategy and core business needs, and in an effort to further strengthen the operational efficiency of its organization, Ironwood commenced a reduction in its workforce by 35 employees, primarily based in the home office. Ironwood completed the reduction in its workforce during the first quarter of 2019. Employees slated to go to Cyclerion were excluded from the workforce reduction; however certain charges associated with the reduction will be allocated to Cyclerion. Ironwood estimates that, in connection with this reduction in

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Notes to the Combined Financial Statements (Continued)

11. Subsequent Events (Continued)

its workforce, it will incur substantially all aggregate charges in the first quarter of 2019 of approximately $3.0 million to approximately $4.0 million for one time employee severance and benefit costs, of which Cyclerion will incur approximately $0.7 million to approximately $0.8 million through corporate allocations. Of these charges, approximately 85% are expected to result in cash expenditures.

On April 1, 2019, Ironwood completed the previously announced separation of its soluble guanylate cyclase business, and certain other assets and liabilities, into a separate, independent publicly traded company by way of a pro-rata distribution of all of the outstanding shares of common stock of Cyclerion Therapeutics, Inc. through a dividend distribution of one share of the Company's common stock, with no par value per share, for every 10 shares of Ironwood common stock held by Ironwood stockholders as of the close of business on March 19, 2019, the record date for the distribution (the entire transaction being the "Separation"). As a result of the Separation, the Company became an independent public company and commenced regular way trading under the symbol "CYCN" on the Nasdaq Global Select Market on April 2, 2019. On April 2, 2019, the Company issued 11,817,165 shares ("Private Placement Shares") of its common stock to accredited investors for gross proceeds of $175.0 million (net proceeds of $165.00 million) pursuant to the Amended and Restated Common Stock Purchase Agreement, dated February 25, 2019. The funds associated with the sale of Private Placement Shares was received by the Company as of April 2, 2019, and as a result, the substantial doubt surrounding the Company's ability to continue as a going concern (as discussed in Note 1) has been alleviated. As of April 2, 2019, the Company, though it expects negative cash flows to continue through 2019 as it continues the development and clinical stage testing of its product candidates and its discovery research programs, expects to be able to fund operating expenses and capital expenditure requirements through the first quarter of 2021.

Peter Hecht, Ironwood's former Chief Executive Officer and the Chief Executive Officer and board member of Cyclerion, donated 2.5 million of his shares of Ironwood common stock to American Endowment Foundation for the creation of a donor advised fund that divested these shares to invest $34.0 million in Cyclerion as part of this financing. Mark Currie, Ironwood's Chief Scientific Officer and future President of Cyclerion and board member of Ironwood, has invested $4.0 million in Cyclerion as part of this financing. Dr. Currie and certain other investors have funded a portion of their investment through sales of Ironwood common stock. Given the aforementioned director and officer affiliations with both Ironwood and Cyclerion, these investments are considered to be related party transactions.

In connection with the Separation, on March 30, 2019, the Company entered into certain agreements with Ironwood to provide a framework for the Company's relationship with Ironwood following the Separation, including, among others, the following agreements:

- Separation Agreement
- Tax Matters Agreement
- Employee Matters Agreement

In addition, in connection with the Separation, on April 1, 2019, the Company entered into a Development Agreement, an Ironwood Transition Services Agreement, a Cyclerion Transition Services Agreement and an Intellectual Property License Agreement with Ironwood.

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Notes to the Combined Financial Statements (Continued)

11. Subsequent Events (Continued)

On April 1, 2019, the Company entered into a direct lease (the "Lease") for its existing operating premises consisting of approximately 114,000 rentable square feet of office and lab space on the first and second floors. The Lease is for a term of 123 months with two five-year extension options and certain expansion rights. The Lease includes a letter of credit of $7.7 million posted with the landlord as a security deposit. Cyclerion has also entered into customary non-disturbance arrangements with the building landlord's mortgagee and with the property ground lessor recognizing Cyclerion's leasehold interest at this property. As part of the Separation, certain improvements are being completed in the Company's leased premises. To accommodate the post-Separation completion of such improvements, on March 31, 2019, the Company entered into a short-term swing space sublease of approximately 24,000 rentable square feet in Ironwood's remaining premises building to allow a portion of the Company's employees to continue to operate while such improvements are completed. The sublease is for an initial one-month term with several one-month extension options. The Company is responsible for completing all work to separate the premises and to improve its directly leased premises.

11,574,058 Shares

Common Stock

April 23, 2019