Creating breakthrough treatments for patients with serious and orphan diseases by harnessing the power of sGC
Safe Harbor Statement

This overview contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, such as statements about the status, structure and timing of our separation from Ironwood; expected timing of clinical data and the filing CTA/IND applications; the size and design of clinical trials; the application of; and potential benefits of sGC stimulators, our strategy, including development and commercialization plans; the size of potential markets for our product candidates and; our expected use of cash. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statements. Applicable risks and uncertainties include those related to our lack of independent operating history; the risk that a separation from Ironwood may adversely impact our ability to attract or retain key personnel; the effectiveness of our development and commercialization efforts; risks generally associated with preclinical and clinical development and formulation development; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; risks and uncertainties pertaining to the efficacy, safety and tolerability of our product candidates; decisions by regulatory authorities; the risk that we may never get sufficient patent protection for our product candidates or that we might not be able to successfully protect such patents; the risks listed under the heading “Risk Factors” and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 and in Ironwood's subsequent SEC filings, including SEC filings related to the proposed separation. These forward-looking statements speak only as of the date of this overview, and Ironwood undertakes no obligation to update these forward-looking statements.

This overview describes the businesses to be transferred to Cyclerion by Ironwood in the separation as if the transferred businesses were Cyclerion’s businesses for all historical periods described. References in this overview to Cyclerion's historical assets, liabilities, product candidates, businesses or activities of Cyclerion’s business are generally intended to refer to the historical assets, liabilities, product candidates, businesses or activities of the transferred businesses as the businesses were conducted as part of Ironwood prior to the separation.
5 programs: on track to deliver 4 clinical data readouts in 2019 including 3 Phase 2 studies, and 2 new drug candidates

Distinctive pharmacology: differentiated, tissue-targeted compounds tailored for intended diseases

Powerful pathway: nitric oxide-sGC pathway is clinically validated with significant untapped potential

Successful sGC/cGMP drug hunters: deep pathway knowledge with record of drug making success

High-momentum company launch
2019 launch year expectations

5. Differentiated programs
4. Clinical studies ongoing
3. Phase 2 readouts
2. New tissue-tailored development candidates
1. Great company launch
**Clinical Data Readouts in 2019 on Differentiated Compounds**

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| **Olinciguat** | Sickle Cell Disease (SCD) | | | | | - Top line data expected in 2H2019  
- Granted Orphan Drug Designation by the US FDA  
- Worldwide rights |
| **Systemic sGC Stimulator** | | | | | | |
| **Praliciguat** | Diabetic Nephropathy (DN) | Heart Failure with Preserved Ejection Fraction (HFpEF) | | | | - DN: Top line data expected in 2H2019  
- HFpEF: Top line data expected in 2H2019  
- Pursue out-licensing after completion of Phase 2 studies  
- Granted Fast Track Designation for HFpEF by the US FDA  
- Worldwide rights |
| **Central Nervous System sGC Stimulator** | | | | | | |
| **IW-6463** | | | | | | - CTA filed in 4Q2018  
- Expect to initiate Phase I study 1Q2019  
- Top line data expected in 2H2019  
- Worldwide rights |
| **Liver-Targeted sGC Stimulator** | | | | | | |
| **Liver** | | | | | | - Development candidate nomination expected in 1H2019 |
| **Lung-Targeted sGC Stimulator** | | | | | | |
| **Lung** | | | | | | - Development candidate nomination expected in 1H2019 |

*Status of programs as of January 7, 2019. Represents ongoing phase of development and does not correspond to the completion of a particular phase.*
Tailoring proven, powerful pharmacology for treatment of serious diseases

A powerful pathway...

• Nitric oxide (NO) signaling plays a central role in real-time physiologic regulation of diverse systems
• Discovery of NO signaling was basis for the 1998 Nobel Prize in Physiology or Medicine
• Clinically validated by approved therapies (NO donors, PDE5 inhibitors, sGC stimulator)

...that Cyclerion is working to harness

• Growing understanding of NO pathway role in health and disease
• Developing differentiated next-generation sGC stimulators uniquely designed to target tissues relevant to the diseases each is intended to treat
• Relevant in diseases both with and without nitric oxide signaling deficiency
• Fortified by deep expertise and IP in sGC stimulation
sGC Stimulators Enhance NO-sGC-cGMP Signaling
NO-cGMP signaling regulates multiple aspects of physiology

**sGC stimulators: differentiated mechanism** to modulate NO-cGMP pathway signaling:

- **Act synergistically** with the NO signaling system: same time and same locations in body vs. acting independently of NO signaling
- **Increase overall pathway signaling** vs. relying on basal signaling
- **Act at a non-redundant node** in the pathway and can act anywhere sGC is expressed to increase cGMP vs. inactivating just one of several mechanisms by which cGMP is degraded
- **Selectively modulate NO signaling** vs. acting across any pathway that increases cGMP

Adapted from Buys et al. 2018. Discovery and development of next generation sGC stimulators with diverse multidimensional pharmacology and broad therapeutic potential. Nitric Oxide 78:72-80
sGC stimulators act synergistically with NO

**In vitro (HEK293 cells)**

- Stimulator + NO donor

EC$_{50}$ ~ 100 nM

EC$_{50}$ ~ 3 µM

**In vivo (rat liver/retrodialysis)**

- Stimulator alone

* p<0.05, *** p<0.001, **** p<0.0001 vs PBS
NO-sGC-cGMP signaling acts through multiple downstream pathways to elicit pharmacological effects.

- **Cyclic Nucleotide Gated Channels**
- **Protein Kinase G**
- **Phosphodiesterases**

**sGC Stimulation Can Increase**
- Local vasodilation / blood flow (e.g., vascular and smooth muscle relaxation)
- Metabolism (e.g., AMPK activation)
- Neuronal health and signaling (e.g., neuroprotection, LTP)

**sGC Stimulation Can Decrease**
- Inflammation (e.g., TNFα signaling, EC activation)
- Fibrosis (e.g., TGFβ signaling)
Cyclerion is working to harness the power of sGC pharmacology in disease-relevant tissues

A pipeline of differentiated molecules

Olinciguat | Praliciguat | IW-6463 | Liver-targeted | Lung-targeted
Each program offers the potential to create differentiated and meaningful clinical value for patients.

- Significant unmet clinical need
- Nitric oxide connection
- A targeted sGC stimulator
- Preclinical evidence
- Clinical trials designed to enable decisions to halt or advance the program
SCD is an orphan disease characterized by a low NO state, with early mortality, serious morbidity and limited number of treatment options.

Olinciguat is an oral, once-daily sGC stimulator that distributes to vasculature and highly perfused organs.

Potential to treat SCD by reducing proportion of sickled cells, decreasing vascular inflammation and cell adhesion, and improving local blood flow.

Preclinically, olinciguat treatment was associated with positive effects on blood flow and vascular inflammation.

Phase 2 STRONG SCD study is ongoing to evaluate safety, PK, PD and develop PRO instrument in patients with SCD; topline data expected 2H2019.
Sickle cell disease: the need

SCD results in severe complications that may include painful vaso-occlusive crises (VOCs), daily symptoms such as chronic pain, fatigue and shortness of breath, as well as progressive damage to organs, including the brain, kidneys, lungs, bones and cardiovascular system.

Patients with SCD have a shortened life expectancy, with an average of 42 years for males and 48 years for females in the US.

SCD patients
~100,000 in U.S.¹
~50,000 in EU²

Sickle cell disease: the nitric oxide connection

Increased hemolysis leads to reduced NO bioavailability and production

Low NO bioavailability results in reduced cGMP production

Reduced cGMP leads to vasoconstriction, vascular inflammation, and endothelial dysfunction

These effects contribute the symptoms and complications of SCD in patients

These combined effects result in accumulated vascular and tissue damage that can lead to pain, organ failure, and shortened life expectancy
We believe olinciguat, by amplifying NO signaling, has the potential to improve daily symptoms, reduce VOC and preserve organ function.
In preclinical models, olinciguat treatment was associated with positive effects on SCD pathology

- Preclinically olinciguat treatment was associated with:
  - Distribution to both the vasculature as well as key organs
  - Higher mRNA expression of the γ-globin subunit of fetal hemoglobin in cultured cells
  - Lower levels of vascular inflammatory markers and improved vascular function in mouse models of inflammation*
  - Decrease in progression of hemolytic anemia in SCD mouse model

*Adhesion can occlude microcirculation and lead to painful VOC and other serious complications
Greater normalized expression of the $\gamma$-globin subunit of fetal hemoglobin in cell culture treated with olinciguat

**Increasing fetal hemoglobin is a clinically validated approach to the treatment of sickle cell disease (i.e. hydroxyurea)**

* 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

**** p<0.0001 vs vehicle
Lower expression of cellular adhesion molecules associated with olinciguat treatment in preclinical model

Reducing vascular inflammation via blockade of specific adhesion receptors is a clinically validated approach to reducing painful crises (i.e. crizanlizumab)
Olinciguat is progressing through clinical development

- **Completed Phase 1 studies in healthy subjects**
  - Confirmed target engagement and proof of pharmacology
  - Dose-proportional pharmacokinetics with profile supportive of once-daily dosing
  - Well-tolerated dose range with no serious adverse events or discontinuations due to adverse events (AE)
- **Granted Orphan Drug Designation for the treatment of sickle cell disease**
- **Initiated Phase 2 study in sickle cell disease; data expected 2H2019**
STRONG SCD: Phase 2 ongoing, topline data expected 2H 2019

PATIENTS:
- Male and female patients with SCD, age 16 – 70 years
- Maintain stable regimen of current medications for SCD
- ~88 patients total

ENDPOINTS:
- Safety, tolerability, pharmacokinetics, pharmacodynamics
- Exploratory endpoints to enable decision making include:
  - Biomarkers of disease activity (HbF levels, anemia, inflammatory markers)
  - Health-related patient-reported outcomes (PRO) including chronic pain and fatigue

Ongoing Phase 2 Study
Placebo  Olinciguat  Olinciguat  Olinciguat
Low dose  Mid dose  High dose
QD, 12 WEEK TREATMENT PERIOD
DN and HFpEF are serious cardiometabolic diseases with high morbidity and mortality; limited / no treatment options.

Well suited for potential treatment of DN and HFpEF by reducing inflammation and fibrosis and enhancing blood flow to relevant tissues.

Positive effects on metabolic parameters, fibrosis, inflammation and renal and cardiac function in preclinical disease models. Metabolic effects demonstrated clinically.

Phase 2 studies in HFpEF and DN are ongoing with 2H 2019 readouts, actively pursuing a global partnership to maximize value for patients and shareholders.

Praliciguat has significant potential in cardio metabolic disease.
Diabetic nephropathy: the need

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.

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.

Significant unmet medical need

DN is progressive, and patients that survive to end-stage renal disease require chronic dialysis treatment or kidney transplant.

Large patient population

1. Ghaderian SB, et al., Diabetes and End-Stage Renal Disease; A Review Article on New Concepts, J Renal Inj Prev. 2015
Diabetic nephropathy: the nitric oxide connection

NO signaling plays a central role in renal physiology

Diabetes is associated with endothelial dysfunction and reduced NO signaling

Defects in NO signaling genetically linked to diabetic nephropathy

The decrease in nitric oxide signaling is associated with the progression of DN

Diabetic nephropathy: our solution

We believe praliciguat will preserve kidney function by restoring and enhancing NO-sGC-cGMP signaling to:

- Improve renal blood flow (autoregulation)
- Reduce inflammation and fibrosis
- Improve insulin sensitivity and lipid profile
- Improve renal endothelial function
Preclinical and clinical data for praliciguat support potential utility in diabetic nephropathy

Praliciguat treatment preclinically was associated with:

• Preservation of kidney function in multiple animal models*, including corresponding effects on inflammation, fibrosis, and metabolism
• Anti-inflammatory and anti-fibrotic effects in vivo, mechanistically separated from hemodynamic pharmacology
• Positive effects on fasting glucose and lipids in ZSF1 rat model of diabetic nephropathy

Praliciguat treatment clinically was associated with:

• Decreases in insulin sensitivity and in plasma LDL cholesterol and triglycerides in Phase 2 study in patients with T2DM and hypertension on standard of care including anti-glycemic medications and RAAS inhibitor

* Dahl salt-sensitive rat model of hypertension and ZSF1 rat model of DN
In a preclinical model of hypertension, renal protective effects were observed in praliciguat-treated animals.

Dahl salt-sensitive rat model

* p<0.05, *** p<0.001, **** p<0.0001 vs High-salt control
Anti-fibrotic effects recapitulated in vitro and mechanistically separated from hemodynamic effects

- Human renal proximal tubule epithelial cells in cell culture

** p<0.001; **** p<0.0001 vs TGFβ-vehicle
In an exploratory Phase 2 study, patients with T2DM with hypertension who received praliciguat on top of standard of care* for two weeks had improvements in multiple metabolic parameters.

*Patients on standard of care including anti-glycemic medications and RAAS inhibitor
Praliciguat is progressing through clinical development

- **Completed Phase 1 studies in healthy subjects**
  - Confirmed target engagement and proof of pharmacology
  - Dose-proportional pharmacokinetics with profile supportive of once-daily dosing
  - Demonstrated large volume of distribution and negligible renal clearance

- **Completed exploratory Phase 2 studies in patients with T2DM and a history of hypertension**
  - Pharmacokinetic/pharmacodynamic profile supportive of once-daily dosing
  - Positive metabolic effects in a relevant patient population
    - Patients on standard of care including anti-glycemic medications and RAAS inhibitor
  - Dosing generally well tolerated; AEs reported in more than 2 patients were mild in severity; one SAE (upper GI hemorrhage) in a patient who had ulcerative esophagitis and previously undiagnosed hiatal hernia, resolved same day and patient recovered completely

- **FDA Fast Track Designation granted for HFpEF**

- **Initiated Phase 2 POC studies in DN and in HFpEF; data expected from both in 2H 2019**
DN Phase 2 trial ongoing, topline data expected 2H 2019

**PATIENTS:**
- Adult patients with type 2 diabetes and DN
- Male and female, age 25 – 75 years
- Stable regimen of anti-glycemic medications and RAAS inhibitors
- ~150 patients total

**ENDPOINTS:**
- Change in urine albumin creatinine ratio (UACR) - *primary*
- Safety – *primary*
- Exploratory assessments include changes in cardiometabolic parameters

**ongoing Phase 2 Study**

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<td>12 WEEK TREATMENT PERIOD</td>
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OLINCIGUAT  PRALICIGUAT
IW-6463 LIVER-TARGETED LUNG-TARGETED
HFpEF: the need

Heart failure remains a rising global epidemic with an estimated prevalence of ~38M individuals globally.

HFpEF comprises 44% - 72% of new heart failure diagnoses and accounts for approximately half of the heart failure hospitalizations, with frequent readmissions.

Large and growing prevalence

Significant unmet need

Five-year mortality rates for patients with HFpEF have been reported to range from 55% - 74%.
HFpEF: the nitric oxide connection

Chronic microvascular inflammation and endothelial dysfunction are thought to contribute to the development of cardiac and skeletal muscle inflammation and subsequent fibrosis.

HFpEF: our solution

We believe that praliciguat will improve symptoms of HFpEF by enhancing NO-sGC-cGMP signaling in the heart and periphery to:

- Improve cardiac blood flow
- Improve oxygen delivery and utilization by skeletal muscle
- Reduce microvascular inflammation and fibrosis
- Reduce cardiac stiffness by increasing titin phosphorylation
- Prevent left ventricular remodeling and disease progression

These improvements are expected to increase functional capacity and improve quality of life for patients with HFpEF and also reduce hospitalizations and mortality.
In a preclinical model of HFpEF, praliciguat treatment was associated with:

• Preservation of cardiac function
• Lower cardiac hypertrophy
• Lower levels of biomarkers of inflammation

Praliciguat was granted Fast Track Designation for the treatment of HFpEF by the FDA
In a preclinical model of heart failure, lower cardiac hypertrophy and markers of inflammation in praliciguat-treated rats

**p<0.01; ****p<0.0001 vs High-salt Control; LV+S=left ventricular free wall plus ventricular septum
Phase 2 study ongoing; topline data expected 2H 2019

PATIENTS:
• Adult patients with HFrEF (EF ≥ 40%)
• Male and female, age ≥ 45 years
• ~184 HFrEF patients total

ENDPOINTS:
• CPET: change in peak VO2 – *primary*
• Safety and tolerability – *primary*
• Change in ventilatory efficiency – *secondary*
• Change in 6-minute walk distance – *secondary*
• # CPET responders – *secondary*
• Patient reported outcomes (KCCQ) – *secondary*
• Metabolic: fasting glucose, HOMA-IR, HbA1c, uric acid, lipids

Ongoing Phase 2

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12 WEEK TREATMENT PERIOD
Multidimensional pharmacology of sGC stimulation is well-suited to target multiple aspects of neurodegenerative disorders.

IW-6463 is being developed as an oral sGC stimulator and has shown preclinical effects on cerebral blood flow, neuroinflammation, neuroprotection, neuronal function.

Our translational trial design gives potential for early proof of CNS pharmacology in Phase 1.

We expect to initiate Phase 1 trial in 1Q2019; topline data expected 2H2019.

IW-6463: first and only CNS penetrant sGC stimulator for treatment of neurodegenerative diseases.
IW-6463 has the potential to address four hallmarks of neurodegenerative diseases.

Addressing these parameters may improve neuronal health and cognition.
Increased blood flow to brain areas associated with memory and arousal in rats treated with IW-6463

- Increased blood flow to areas associated with memory and arousal in normal rats by fMRI BOLD imaging -

Note: data provided in this slide is based on preclinical models
Anti-inflammatory neuroprotective effects in mice treated with IW-6463

- Increased cGMP and pCREB in rat brain 3D microtissues -
- Decreased inflammatory cytokines in rodent microglial cultures and brain 3D microtissues -

Note: data provided in this slide based on IW-6463 pretreatment in preclinical models
Neuroprotective effects in mice treated with IW-6463

- Synaptic spine density in aged mice at same level observed in young mice -

Note: data provided in this slide is based on preclinical models
Improved cognitive function in rats treated with IW-6463

Thigmotaxis: tendency to stay close to walls when exploring open spaces, which is associated with cognitive dysfunction and interferes with maze solving.

- Positive effect on cognitive function in multiple animal models, including both aged and pharmacologically impaired rats -

Note: data provided in this slide is based on preclinical models
Cortical brain activity greater in rats treated with IW-6463

- Opportunity for Early Clinical Proof of Pharmacologic Effects –

- Pharmacological effects of IW-6463 can be assessed clinically using translational non-invasive methods including EEG, MRS, ASL, and fMRI BOLD -

Note: data provided in this slide is based on preclinical models
Expect to initiate first in human studies in Q1 2019

The IW-6463 Phase 1 trial is designed to provide early proof of pharmacology

- Safety, tolerability and pharmacokinetic data on single and multiple ascending doses of IW-6463 will be evaluated

- Evaluate the effects of IW-6463 by using quantitative, objective measures of brain activity including:
  - Quantitative EEG
  - A select battery of well characterized cognitive and motor assessments

- This Phase 1 study is designed to translate our observed preclinical effects to humans, potentially demonstrating proof of pharmacology
Liver-targeted sGC stimulator to maximize the potential to treat serious liver diseases

Chronic liver diseases are serious diseases associated with pathologic inflammation and fibrosis and lead to significant morbidity and mortality.

We have designed sGC stimulators that specifically target the liver.

This provides the opportunity to maximize hepatic sGC pharmacology with little or no effect on systemic hemodynamics.

We expect to nominate a development candidate in 1H2019.
There is a clear role for NO-sGC-cGMP signaling in serious pulmonary diseases; sGC stimulation is a clinically validated approach for treatment of Pulmonary Arterial Hypertension (PAH)*

We have designed inhaled sGC stimulators that are lung retentive and lung stable with rapid systemic clearance

This provides the opportunity to maximize pulmonary sGC pharmacology with little or no effect on systemic hemodynamics

We expect to nominate a development candidate in 1H2019

*Lung-targeted sGC stimulator to maximize the potential to treat serious pulmonary diseases

*Adempas® (riociguat) approved for the treatment of PAH
Cyclerion Leadership

Mark Currie, PhD - President
- Extensive research in cGMP signaling pathways and related pharmacology
- Primary inventor of LINZESS, led discovery/pharmacology for Celebrex and Lunesta

Mark Gaffney - Head of External Innovation & Corporate Development
- >12 years experience structuring and negotiating licensing arrangements, partnerships and acquisitions

Cheryl Gault - Head of Strategy
- >15 years marketing, sales, new product planning, commercial strategy at Ironwood and Genzyme

Chris Wright, MD, PhD - Head of Development
- >20 years drug development in rare and orphan diseases; oversaw clinical development of Orkambi and Kalydeco
- Practicing neurologist at Brigham & Women’s Hospital

Peter Hecht – CEO
- >20 years CEO experience – co-founder of Microbia/IRWD
- Under his leadership, Ironwood has grown from nine Ph.D. scientists to a commercial biotechnology company

Bill Huyett - CFO
- 30-year career at McKinsey and Co
- Extensive experience in pharma/med device corporate strategy, capital allocation, finance, product development and commercialization, and corporate leadership

Anjeza Gjino - Head of Finance
- >13 years of finance experience leading and supporting capital allocation and business transformation initiatives at Ironwood and PerkinElmer

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Separation: Cyclerion ready to launch 1H 2019

Right leadership, right time

- Peter Hecht to be Cyclerion CEO effective upon separation
- Experienced leadership team complemented with new skills
- Expected to have a non-overlapping board with Ironwood
- Board (including new Chair) expected to be announced in next 60 days

Well-structured

- Cyclerion expected to raise $150-200M equity (~8-12 quarters of funding) to launch; fits broad shareholder feedback that it raise capital with equity & partnerships
- Expected tax-free distribution of Cyclerion common stock to IRWD shareholders
- No expected ongoing funding from Ironwood
Sequence of the planned sponsored spin separation

- **Separation announcement**
  - Design financing
  - Build sponsor investor book
  - Form 10 registration statement filed and effective
  - Distribute CYCN shares to IRWD shareholders and receive equity investment from sponsor investors

Operating and trading as independent companies