Pipeline

Olinciguat
Vascular sGC Stimulator

Discovery | IND Enabling | Phase 1 | Phase 2 | Phase 3

Pharmacologically tailored for sickle cell disease (SCD)

Olinciguat is an orally administered, once-daily, vascular sGC stimulator designed for the treatment of sickle cell disease (SCD). SCD is a genetic disorder of the hemoglobin, with blood vessel and multi-organ involvement. As such, we believe the distribution of olinciguat to the vasculature as well as to organs with high blood flow, such as the kidney and lungs, makes it particularly well suited for the potential treatment of SCD.

By amplifying nitric oxide signaling, we believe that olinciguat has the potential to:

1.) Improve local blood flow to organs
1.) Reduce vascular inflammation
1.) Reduce the proportion of sickled cells

Clinical Development Status and Late Stage Development Strategy

Olinciguat has been granted Orphan Drug Designation for SCD by the U.S. Food and Drug Administration and is currently in a Phase 2 study in patients with SCD, the STRONG-SCD study. We expect results from this study in mid-2020.

Following the completion of our ongoing Phase 2 study, should data warrant, we intend to rapidly advance olinciguat into late-stage development for SCD.

Commercialization Strategy

If approved, we intend to commercialize olinciguat on our own in the United States and alone, or through licensing arrangements, with partners around the world.

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Granted Orphan Drug Designation for SCD by the US Food and Drug Administration (FDA)

Phase 2 data expected in mid-2020

Praliciguat
Systemic sGC Stimulator

Discovery | IND Enabling | Phase 1 | Phase 2 | Phase 3

Pharmacologically tailored for serious cardiometabolic diseases

Praliciguat is an orally administered, once-daily systemic sGC stimulator designed for the treatment of serious cardiometabolic diseases such as Diabetic Nephropathy, or DN. In a preclinical study, oral praliciguat demonstrated extensive distribution to adipose tissue, kidney, heart and liver, and the extensive distribution of praliciguat has been confirmed in clinical studies. We believe this 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.

Clinical Development Status

Cyclerion completed two Phase 2 studies of praliciguat in patients with diabetic nephropathy and in patients with heart failure with preserved ejection fraction (HFpEF).

The diabetic nephropathy study showed a trend toward improvement across the total intention-to-treat (ITT) study population on its primary endpoint of reduction in albuminuria from baseline as compared to placebo, measured by urine albumin creatinine ratio (UACR), but did not meet statistical significance. In a post-hoc sensitivity analysis, we evaluated the results in a modified ITT in which data from one clinical trial site, which were found to be inconsistent with those of the overall study population, were excluded. In this analysis, an increased treatment effect and reduced variability were observed.

In addition, improvements were observed in diabetic nephropathy patients treated with praliciguat in several secondary vascular and metabolic measures associated with cardiovascular risk and kidney disease progression, including blood pressure, cholesterol and HbA1c levels, compared to placebo. All patients were on concomitant stable standard of care therapy, including anti-diabetic medications and renin-angiotensin-aldosterone system (RAAS) blockers. As in prior clinical studies, the pharmacokinetic profile of praliciguat was consistent with once-daily dosing. Praliciguat was generally well tolerated, and the safety profile was supportive of continued development.

The HFpEF study did not meet statistical significance on its primary endpoint of improved exercise capacity from baseline as compared to placebo, measured by cardiopulmonary exercise testing (CPET). There was clear evidence of drug exposure and pharmacological activity as judged by expected reductions in blood pressure. Praliciguat was generally well tolerated, and the safety profile supported investigation of praliciguat in other indications. Based on these results, Cyclerion discontinued development of praliciguat in HFpEF.

Late-Stage Clinical Development & Commercialization Strategy

We are pursuing out-license of praliciguat for late-stage development and commercialization in DN.

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Granted Fast Track Designation for HFpEF by the U.S. Food & Drug Administration (FDA)

Phase 2 data for HFpEF and for DN expected in 2H 2019

IW - 6463
Central Nervous System sGC Stimulator

Discovery | IND Enabling | Phase 1 | Phase 2 | Phase 3

Pharmacologically tailored for serious neurodegenerative diseases

IW-6463, which we believe is the first and only central nervous system (CNS)-penetrant sGC stimulator to enter clinical trials, is pharmacologically tailored to address neurodegenerative diseases. Nitric oxide is a fundamental neurotransmitter with demonstrated impact on memory and cognition. Its role in neural function was discovered in the late 1970s, but until now there has not been an opportunity to leverage this mechanism to potentially enhance CNS functioning and treat disease. 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 enhance cognition and combat neurodegeneration via the neuroprotective and neurofunctional benefits of nitric oxide signaling.

In preclinical studies, IW-6463 demonstrated significant exposure in the CNS. Treatment with IW-6463 was associated with increases in cerebral blood flow, reductions in markers of neuroinflammation, increased neuroprotection and enhanced cognition across a variety of preclinical models.

Clinical Development Status

We completed a Phase 1 first-in-human study in Q4 2019. The three-stage study evaluated: a) single ascending doses, b) multiple ascending doses (over 14 days) and c) food interaction effects. Study results demonstrated that IW-6463 was well tolerated across the tested dose levels. PK data obtained from the CSF demonstrate penetration of IW-6463 into the CNS at levels expected to be pharmacologically active. Food interaction results indicate that IW-6463 may be taken with or without food.

A Phase 1 translational pharmacology study in elderly subjects is ongoing. This study will evaluate safety, PK, and measures of CNS pharmacological activity, including cerebral blood flow by MRI and additional translational measures. Topline study results are expected in mid-2020.

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Translational pharmacology study results expected in mid-2020

Liver
Liver-targeted sGC Stimulator

Discovery | IND Enabling | Phase 1 | Phase 2 | Phase 3

Pharmacologically tailored to address serious and orphan liver diseases

Our liver-targeted sGC stimulator will be orally administered and designed to selectively partition to the liver. In preclinical 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. By achieving liver concentrations many fold higher than corresponding plasma concentrations, we intend to maximize hepatic pharmacology.

Lung
Lung-targeted sGC Stimulator

Discovery | IND Enabling | Phase 1 | Phase 2 | Phase 3

Pharmacologically tailored to address serious and orphan pulmonary diseases

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, our lead molecule is metabolically stable in the lung, whereas it is unstable in the plasma with rapid systemic clearance.

*Status of sGC programs as of January 13, 2020. Represents ongoing phase of development, does not correspond to the initiation or completion of a particular phase.

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