Ironwood Pharmaceuticals Initiates Phase 1 Trial of IW-6463, the First CNS-penetrant sGC Stimulator to Enter Clinical Trials

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– IW-6463 is one of five Cyclerion sGC stimulators following planned separation –

– Data from Phase 1 study expected in second half of 2019 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 23, 2019-- Ironwood Pharmaceuticals, Inc. (Nasdaq: IRWD) today announced the initiation of a Phase 1 study evaluating IW-6463 in healthy volunteers. IW-6463 is an orally administered central nervous system (CNS)-penetrant soluble guanylate cyclase (sGC) stimulator that is being developed for the treatment of serious and orphan CNS disorders. Data from the Phase 1 study are expected in the second half of 2019.

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"The initiation of this Phase 1 study with IW-6463 marks an important milestone for our portfolio of next-generation sGC stimulators," said Chris Wright, M.D., Ph.D., Ironwood's current head of development and incoming chief medical officer and head of development of Cyclerion Therapeutics, Inc. (Cyclerion). "With its ability to cross the blood-brain-barrier, we believe IW-6463 may represent an important option for the treatment of serious neurodegenerative diseases, where there is a high unmet medical need. Our Phase 1 study is designed to provide safety, tolerability and pharmacokinetic data on single- and multiple-ascending doses of IW-6463, as well as to explore evidence of translation of some of our pre-clinical results on CNS activity in this first-in-human study."

The randomized, placebo-controlled Phase 1 clinical study is designed to assess the safety, tolerability, and pharmacokinetics of oral IW-6463 in healthy volunteers. The study will evaluate both single-ascending and multiple-ascending doses of IW-6463 in healthy subjects using a randomized, placebo-controlled, double-blind, sequential-group design.

IW-6463 is one of five differentiated sGC stimulator programs expected to be advanced by Cyclerion, a clinical-stage biopharmaceutical company focused on breakthrough treatments for serious and orphan diseases. The separation of Ironwood and Cyclerion is on track to be completed in the first half of 2019.

About IW-6463

sGC stimulators are small molecules that act synergistically with nitric oxide on sGC to boost production of cyclic guanosine monophosphate (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, inflammation and fibrosis, metabolism and neuronal function. Cyclerion expects to advance a portfolio of five sGC stimulators, each designed to target tissues most relevant to the diseases they are intended to treat. As an orally administered sGC stimulator that has been shown pre-clinically to readily cross the blood-brain barrier, IW-6463 presents the 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, 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 be employed in clinical studies.

About Cyclerion Therapeutics

Cyclerion Therapeutics is a clinical-stage biopharmaceutical company harnessing the power of sGC pharmacology to discover, develop and commercialize breakthrough treatments for serious and orphan diseases. Cyclerion plans to advance its portfolio of five differentiated sGC stimulator programs with distinct pharmacologic and biodistribution properties that are uniquely designed to target tissues of greatest relevance to the diseases they are intended to treat. These programs, each of which have important milestones in 2019, include olinciguat in Phase 2 development for sickle cell disease, praliciguat in Phase 2 trials for heart failure with preserved ejection fraction (HFpEF) and for diabetic nephropathy, IW-6463 in Phase 1 development for serious and orphan central nervous system diseases, and two late-stage discovery programs targeting serious liver and lung diseases, respectively.

About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (Nasdaq: IRWD) is a commercial biotechnology company focused on creating medicines that make a difference for patients, building value for our fellow shareholders, and empowering our passionate team. We discovered, developed and are commercializing linaclotide, the U.S. branded prescription market leader for adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC). Our pipeline priorities for linaclotide include a Phase IIIb trial evaluating its efficacy and safety on multiple abdominal symptoms, including abdominal bloating, pain, and discomfort in adult patients with IBS-C, as well as research into a formulation of linaclotide designed to relieve abdominal pain associated with IBS.

We are also advancing a pipeline of innovative product candidates in areas of significant unmet need, including persistent gastroesophageal reflux disease, and the product candidates that Cyclerion expects to advance following completion of the planned separation of Ironwood and Cyclerion into two independent, publicly-traded companies. The separation is expected to be completed in the first half of 2019. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. For more information, please visit www.ironwoodpharma.com or www.twitter.com/ironwoodpharma; information that may be important to investors will be routinely posted in both these locations.

Forward-Looking Statements

This press release contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements about the design and scope of the Phase 1 study of IW-6463; the expected timing of the data from the Phase 1 study; the proposed separation of our operations into two independent, publicly traded companies, including the status, structure, completion and timing of the separation; the business and operations of Ironwood and Cyclerion and the benefits of a potential separation, including with respect to Ironwood's and Cyclerion's competitive position, attractiveness to investors and enhanced operational, commercial and scientific effectiveness; and the leadership of Cyclerion following the separation. 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 statement. Applicable risks and uncertainties include those related to preclinical and clinical development, manufacturing and formulation development; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of our product candidates; decisions by regulatory and judicial authorities; the risk that we are unable to successfully commercialize our product candidates; the risk that we may never get sufficient patent protection for product candidates or that we are not able to successfully protect such patents; the outcomes in legal proceedings to protect or enforce the patents relating to our products and product candidates; developments in the intellectual property landscape; challenges from and rights of competitors or potential competitors; the possibility that we may not complete the separation on the terms or timeline currently contemplated, if at all; that neither Ironwood nor Cyclerion may achieve the expected benefits of a separation, and that a separation could harm the business, results of operations and financial condition of Ironwood and Cyclerion; the risk that we may be unable to make, on a timely or cost-effective basis, the changes necessary to operate as independent companies; Cyclerion's lack of independent operating history and the risk that its accounting and other management systems may not be prepared to meet the financial reporting and other requirements of operating as an independent public company; the risk that a separation may adversely impact Ironwood's and Cyclerion's ability to attract or retain key personnel; the risk that the management of Cyclerion will be different than currently contemplated; and 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. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Ironwood and Cyclerion undertake no obligation to update these forward-looking statements.

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