Rhythm Pharmaceuticals Announces Acquisition of Xinvento B.V. and Portfolio of Investigational Therapeutics

February 27, 2023

- Rare disease company in preclinical development for congenital hyperinsulinism -

- Acquisition is strong strategic fit with Rhythm's rare endocrinology focus and provides meaningful new development opportunity -

- Expect to initiate clinical development in 2024 -

BOSTON and AMSTERDAM, Feb. 27, 2023 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases, today announced that Rhythm's Netherlands subsidiary, Rhythm Pharmaceuticals Netherlands B.V. ("Rhythm BV"), acquired Xinvento B.V., a Netherlands-based biotech company focused on developing therapies for congenital hyperinsulinism (CHI). CHI is a rare genetic disease in which cells secrete excess insulin, causing hypoglycemia, which can result in serious health outcomes including seizures, coma, permanent brain damage and death.

Xinvento was founded in 2021 by Claudine van der Sande, an experienced biopharmaceutical leader who previously held positions at Roche and Sanofi, and whose first-hand experience as a caregiver to her son living with CHI inspired her mission to seek a more effective treatment for CHI patients. Ms. van der Sande partnered with Dr. Piet Wigerinck, a medicinal chemist who served as chief scientific officer of Galapagos for 10 years, to lead the scientific effort. Xinvento is developing novel investigational therapeutic candidates designed to improve the care of patients with CHI.

Following the closing of this acquisition, Ms. van der Sande, Founder and CEO of Xinvento, will join Rhythm as Vice President, Head of CHI program, and will provide her deep subject matter expertise to the advancement of the CHI program.

"As a mother and primary caregiver to a child with CHI, Claudine knows that there is significant unmet need for new treatment options that can safely lower the frequency of hypoglycemic events and help minimize the incidence of irreversible brain damage in people born with CHI. In two short years, we believe she has driven a nimble, science-focused organization towards bringing a highly promising therapeutic candidate into the clinic," said David Meeker, M.D., Chair, President and Chief Executive Officer of Rhythm. "We are excited for the opportunity to expand our pipeline into CHI, a rare disease that is well aligned with our corporate strategy and our focus on rare endocrinology indications. We look forward to entering the clinic with a new therapeutic candidate in 2024."

"I am confronted daily with the constant challenges and fears of living with CHI and the urgent need for an effective new treatment. I believe Rhythm's deep clinical development, regulatory and commercial experience in rare diseases makes it the ideal partner to accelerate Xinvento's CHI program," said Ms. van der Sande. "I'm thrilled to join the Rhythm team to continue our work to bring a new therapy to patients and families who need improved options to treat this difficult, chronic disease."

According to the terms of the acquisition agreement, Rhythm B.V. will purchase 100 percent of Xinvento's fully-diluted equity for an upfront payment of $5 million (subject to customary adjustments) with an additional payment of up to $6 million in preclinical development milestones and up to an additional $50 million payable upon certain U.S. or EU regulatory approvals. Rhythm B.V. will also pay up to an additional $150 million in certain commercial net sales milestones related to the lead candidate or a second molecule, in the event a second molecule is selected, developed and approved.

About Congenital Hyperinsulinism
Congenital hyperinsulinism (CHI) is the most frequent cause of severe, random and persistent hypoglycemia in newborns and children. Hypoglycemia results from a dysregulation of insulin, which causes blood sugar levels to fall dangerously low. Without proper and immediate treatment, children with CHI may suffer seizures, coma, or even death and, longer term, patients may experience developmental delays, epilepsy, cerebral palsy, and other neurological damage. The estimated incidence rate for CHI is 1:29,000 to 1:31,000, according to the literature.[1]

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) pathway diseases. Rhythm's lead asset, IMCIVREE (setmelanotide), an MC4R agonist designed to treat hyperphagia and severe obesity caused by these diseases, is

approved by the U.S. Food and Drug Administration (FDA) for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing, or patients with a clinical diagnosis of Bardet-Biedl syndrome (BBS). Both the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare MC4R pathway diseases, as well as a preclinical suite of small molecules for the treatment of congenital hyperinsulinism. Rhythm's headquarters is in Boston, MA.

Setmelanotide Indication
In the United States, setmelanotide is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to POMC, PCSK1 or LEPR deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1 or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) or BBS.

In the European Union, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) or genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

Limitations of Use
In the United States and Europe, Setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1 or LEPR deficiency with *POMC*, *PCSK1* or *LEPR* variants classified as benign or likely benign
- Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity.

WARNINGS AND PRECAUTIONS

Skin Monitoring: Setmelanotide may lead to generalized increased skin pigmentation and darkening of pre-existing naevi because of its pharmacologic effect. Full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmentary lesions before and during treatment with setmelanotide.

Heart rate and blood pressure monitoring: Heart rate and blood pressure should be monitored as part of standard clinical practice at each medical visit (at least every 6 months) for patients treated with setmelanotide.

Prolonged penile erection: Spontaneous penile erections have been reported in clinical trials with setmelanotide. Patients who have a penile erection lasting longer than 4 hours should be instructed to seek emergency medical attention for potential treatment of priapism.

Depression: In clinical trials, depression has been reported in patients treated with setmelanotide. Patients with depression should be monitored at each medical visit during treatment with setmelanotide. Consideration should be given to discontinuing setmelanotide if patients experience suicidal thoughts or behaviors.

Pediatric Population: The prescribing physician should periodically assess response to setmelanotide therapy. In growing children, the impact of weight loss on growth and maturation should be evaluated. The prescribing physician should monitor growth (height and weight) using age- and sex-appropriate growth curves.

Excipients: This medicinal product contains 10 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Patients who are pregnant or breastfeeding should be advised of the potential risk from the excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. This medicinal product should be used with caution in patients with hepatic or renal impairment, because of the potential risk from the excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free."

ADVERSE REACTIONS
The most frequent adverse reactions are hyperpigmentation (51%), injection site reaction (39%), nausea (33%), and headache (26%).

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data from the use of setmelanotide in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. However, administration of setmelanotide to pregnant rabbits resulted in decreased maternal food consumption leading to embryo-foetal effects. As a precautionary measure, setmelanotide should not be started during pregnancy or while attempting to get pregnant as weight loss during pregnancy may result in fetal harm. If a patient who is taking setmelanotide has reached a stable weight and becomes pregnant, consideration should be given to maintaining setmelanotide treatment as there was no proof of teratogenicity in the nonclinical data. If a patient who is taking setmelanotide and still losing weight gets pregnant, setmelanotide should either be discontinued, or the dose reduced while monitoring for the recommended weight gain during pregnancy. The treating physician should carefully monitor weight during pregnancy in a patient taking setmelanotide.

Breast-feeding
It is unknown whether setmelanotide is excreted in human milk. A nonclinical study showed that setmelanotide is excreted in the milk of nursing rats. No quantifiable setmelanotide concentrations were detected in plasma from nursing pups. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from setmelanotide therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Fertility
No human data on the effect of setmelanotide on fertility are available. Animal studies did not indicate harmful effects with respect to fertility.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337. See Summary of Product Characteristics' APPENDIX V for a list of European national reporting systems to communicate adverse reactions.

Please see the full Prescribing Information for additional Important Safety Information.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the potential and anticipated benefits of our acquisition of Xinvento BV, the potential of novel investigational therapeutic candidates to treat CHI and anticipated clinical development timeline for a therapeutic candidate, and management changes. Statements using word such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional product candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, the impact of competition, inability to maintain our collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, the impact of the COVID-19 pandemic and general economic conditions on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, failure to realize the anticipated benefits of our acquisition of Xinvento B.V. or significant integration difficulties related to acquisition, and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2022 and our other filings with the Securities and Exchange Commission.. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

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[1] Yau PLoS ONE 15(2): e0228417 https://doi.org/10.1371/journal.pone.0228417 and J Diabetes Investig 2020; 11: 554–563 doi: 10.1111/jdi.13180

Source: Rhythm Pharmaceuticals, Inc.