Rhythm Pharmaceuticals and RareStone Ltd. Announce Exclusive Licensing Agreement for the Development and Commercialization of IMCIVREE (setmelanotide) in China

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-- RareStone to seek marketing authorization for IMCIVREE to treat obesity due to biallelic POMC, PCSK1 and LEPR deficiencies and Bardet-Biedl and Alström syndromes in mainland China, Hong Kong and Macau --
-- Rhythm to receive $12 million upfront in cash and equity, up to $63.5 million in future milestone payments and sales royalties --

BOSTON, Dec. 06, 2021 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic diseases of obesity, and RareStone LTD, formerly Citrine Medicine, a China-based rare disease company, today announced an exclusive licensing agreement for the development and commercialization of IMCIVREE® (setmelanotide) in China, including mainland China, Hong Kong and Macau. This licensing agreement marks the first expansion of Rhythm's pipeline into Asia and is designed to accelerate patient access to IMCIVREE where there remains significant unmet need to address the severe, early-onset obesity and hyperphagia that characterize both acquired and genetic diseases of the melanocortin-4 receptor (MC4R) pathway.

According to the terms of the agreement, RareStone will seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to biallelic proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency, as well as Bardet-Biedl and Alström syndromes. Additionally, RareStone will fund efforts to identify and enroll patients from China in Rhythm's global EMANATE trial, a Phase 3, randomized, double-blind, placebo-controlled trial to evaluate setmelanotide in five independent sub-studies in patients with obesity due to a heterozygous variant of POMC/PCSK1 or LEPR; certain variants of the SRC1 gene, certain variants of the SH2B1 gene, or PCSK1 N221D deletions within the MC4R pathway.

"RareStone, a company committed to treating rare diseases, is well-positioned to leverage its network of hospitals and key opinion leaders, deep regulatory experience and community-building infrastructure to advance IMCIVREE through clinical development and regulatory approvals in China," said David Meeker, M.D., Chair, Chief Executive Officer and President of Rhythm. "We are thrilled to enter into this agreement, which substantially accelerates our ability to address the needs of patients living in China and potentially make IMCIVREE available to many more patients with rare genetic diseases of obesity."

RareStone was founded in 2019 with funding from leading health care investors, including Eight Roads, F-Prime Capital, Vivo Capital, Quan Capital, 3H Health Investment and WU Capital. The Shanghai-based company is focused on building an ecosystem to support patients and families living with rare diseases in Greater China and has dedicated itself to improving the lives of patients with rare and intractable diseases by making diagnosis and essential treatments available and accessible to those who need them.

"There is a significant need in China for a therapeutic option to treat patients with early-onset, severe obesity and hyperphagia caused by variants in genes of the MC4R pathway," said Shawn Xiang, Ph.D., CEO of RareStone. "Rhythm's precision medicine, IMCIVREE (setmelanotide), approved by FDA and authorized by the European Commission and Great Britain's Medicines & Healthcare Products Regulatory Agency, has transformed the treatment paradigm for rare genetic diseases of obesity. We are eager to deliver the proven clinical benefit of IMCIVREE to patients in China and plan to pursue local approvals rapidly in five initial indications, while supporting Rhythm's ongoing clinical development efforts more broadly."

According to the terms of the licensing agreement, RareStone will make an upfront payment to Rhythm of $7 million and issue $5 million in equity to Rhythm. Rhythm will be eligible to receive development and commercialization milestones of up to $63.5 million, as well as tiered royalty payments on annual net sales of IMCIVREE.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. Rhythm's precision medicine, IMCIVREE (setmelanotide), was approved in November 2020 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 obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing and in July and September 2021, respectively, by the European Commission (EC) and Great Britain's Medicines & Healthcare Products Regulatory Agency (MHRA) for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above.

IMCIVREE is the first-ever FDA-approved and EC- and MHRA-authorized therapy for patients with these rare genetic diseases of obesity. The Company submitted a supplemental New Drug Application (sNDA) to the FDA, which was accepted for filing in November 2021 and assigned a Prescription Drug User Fee Act (PDUFA) goal date of March 16, 2022. Rhythm also submitted a Type II variation application to the European Medicines Agency in October 2021 seeking regulatory approval and authorization for setmelanotide to treat obesity and control of hunger in adult and pediatric patients 6 years of age and older with BBS or Alström syndrome in both the United States and European Union. Additionally, Rhythm, along with its partners, is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity and is leveraging the Rhythm Engine, the largest known obesity DNA database -- now with approximately 45,000 sequencing samples -- to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies. Rhythm's headquarters is in Boston, MA.

About RareStone LTD.
RareStone, formerly Citrine Medicine, is dedicated to improving the lives of patients with rare and intractable diseases by making diagnosis and essential treatments available and accessible to those who need them in Greater China. Our mission is to build the first rare disease ecosystem in China, and in doing so, enable people with rare diseases to live more normal lives. In addition to developing and marketing rare disease drugs, RareStone aims to establish a patient-centric platform which educates people on rare diseases, trains doctors on diagnosis and treatment, and helps doctors develop a full disease management protocol. RareStone's lead product candidate, Wakix ® (pitolisant), is an investigational oral drug in development for the treatment of narcolepsy and obstructive sleep apnea in China. RareStone also recently announced two strategic partnerships that will gives the company exclusive Greater China rights to develop, register, and commercialize Alkindi® for pediatric congenital adrenal hyperplasia (CAH) patients and Efmody® for adolescent and adult CAH and adrenal insufficiency patients. RareStone is headquartered in Shanghai, China and has other offices in Beijing, China and Cambridge, Mass. For more information, visit www.rarestonegroup.com

IMCIVREE® (setmelanotide) Indication
In the United States, IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by an FDA-approved genetic test demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

In the EU and Great Britain, IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 6 years of age and above. IMCIVREE should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use
IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE 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, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Important Safety Information

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Sexual adverse reactions may occur in patients treated with IMCIVREE. Spontaneous penile erections in males and sexual adverse reactions in females occurred in clinical studies with IMCIVREE. Instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Some drugs that target the central nervous system, such as IMCIVREE, may cause depression or suicidal ideation. Monitor patients for new onset or worsening of depression. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors.

Skin Pigmentation and Darkening of Pre-Existing Nevi: IMCIVREE may cause generalized increased skin pigmentation and darkening of pre-existing nevi due to its pharmacologic effect. This effect is reversible upon discontinuation of the drug. Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary lesions**.**

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants.

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and

spontaneous penile erection.

USE IN SPECIFIC POPULATIONS
Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Treatment with IMCIVREE is not recommended for use while breastfeeding.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See U.S. Full Prescribing Information, EU SmPC and MHRA SmPC for IMCIVREE.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the 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 activities in connection with the exclusive licensing agreement with RareStone and potential payments thereunder, the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of clinical trials and release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and timing thereof, and our business strategy and plans, including regarding commercialization of setmelanotide. 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 impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our liquidity and expenses, the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, 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, 2021 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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