Rhythm Pharmaceuticals Provides Update on Research and Development Programs

September 25, 2019

-- Four new MC4R pathway obesity indications added to Phase 2 Basket Study and enrolling patients --

-- Genetic sequencing of 13,567 individuals with severe obesity yields 11.7 percent (1,584 individuals) who have a rare genetic variant within MC4R pathway eligible for Phase 2 Basket Study --

-- Sequencing results supports ultra-rarity of POMC and LEPR deficiency obesity --

-- Sequencing results suggest U.S. prevalence estimates for four new indications of greater than 60,000 --

-- Updated data from continuing patients with Bardet-Biedl syndrome in Phase 2 Basket trial demonstrate 22.2 percent mean weight loss following approximately two years on therapy --

-- Rhythm R&D event in New York City; Live webcast begins at 8:15 a.m. today --

BOSTON, Sept. 25, 2019 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq:RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic disorders of obesity, today will announce an update on its Research & Development (R&D) programs, genetic sequencing efforts and patient finding initiatives at its R&D event in New York City.

During the event, the Company will provide a comprehensive overview of the four new melanocortin-4 receptor (MC4R) pathway-driven disorders that it has added to its Phase 2 Basket Study, as well as updated U.S. prevalence estimates for all of the MC4R pathway-driven rare genetic disorders of obesity for which it is currently evaluating setmelanotide. The Company also will share updated data from its Phase 2 Basket Study of setmelanotide in Bardet-Biedl syndrome (BBS) and Alström syndrome and provide details on ongoing community building and patient-finding efforts related to those two indications. Together, the presentations will highlight how the Rhythm Engine is working to discover disease-causing genetic variants and sequence patients to identify those living with MC4R pathway-driven disorders of obesity and potentially provide these patients with the first disease-modifying therapeutic option.

“In collaboration with partners, patients and health care providers, Rhythm is advancing toward our goal of changing the paradigm for rare genetic disorders of obesity,” said Keith Gottesdiener, M.D., Chief Executive Officer of Rhythm. “We are committed to advancing the science underlying MC4R-pathway obesity disorders and expanding our clinical development and community-building efforts. Through these initiatives, we aim to provide patients with severe obesity and unrelenting hunger a potential new therapeutic option, and to equip physicians and caregivers with the knowledge and resources to better manage these disorders.”

Expansion of the Rhythm Basket Study into Four Additional Indications

Rhythm is expanding its Phase 2 Basket Study into four new indications: SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome obesity. The Company is evaluating setmelanotide for the treatment of severe obesity and unrelenting hunger, or hyperphagia, associated with these diseases.

- ***SRC1 deficiency obesity*****:** SRC1 is a transcriptional coactivator that drives pro-opiomelanocortin (POMC) expression.
- ***SH2B1 deficiency obesity*****:** SH2B1 is an adapter protein that regulates leptin receptor (LEPR) activity.
- ***MC4R deficiency obesity:*** The MC4R is the receptor for POMC ligands, and is responsible for the satiety effects of α/β-MSH. The Company plans to focus its development efforts on patients with potentially rescuable variants in the MC4R.
- ***Smith-Magenis syndrome (SMS) obesity****:* SMS is caused by dysfunction of the RAI1 gene, a transcription factor for a number of MC4R pathway genes, which affects POMC expression.

“We are taking an exciting step toward our foundational goal of translating our understanding of the MC4R pathway into treatments for people living with rare genetic disorders of obesity,” said Alastair Garfield, Ph.D., Vice President of Translational Research and Development of Rhythm. “Leveraging our extensive scientific expertise, genetic sequencing initiatives and variant interpretation capabilities, we selected additional rare genetic disorders of obesity to include in our Phase 2 Basket Study, each with a strong scientific tie to the MC4R pathway and, we believe, a larger target population than certain other indications that we are currently evaluating in clinical trials. We look forward to evaluating setmelanotide in these indications in the months and years ahead. We are also committed to continuing to probe the numerous other MC4R pathway genes that may be implicated in rare

genetic disorders of obesity and may provide additional opportunities for setmelanotide."

Genetic Sequencing Provides Updated U.S. Prevalence Estimates for Genetically-identified MC4R Pathway-driven Indications

Rhythm has been collaborating with partners to advance its own initiatives to sequence individuals living with early-onset, severe obesity to uncover more rare genetic disorders of obesity, and develop a better understanding of those disorders currently under study in its pivotal trials and Phase 2 Basket Study. As of June 2019, the Company collected samples from 13,567 individuals with severe obesity, and those samples have yielded 11.7 percent, or 1,584 genetically-identified individuals, who have a rare genetic variant of the MC4R pathway and who may be eligible for inclusion in Rhythm's Phase 2 Basket Study or Rhythm's pivotal Phase 3 trials.

Rhythm's genetic sequencing results have identified samples from 29 patients with POMC or LEPR deficiency obesity. This result supports that these conditions are ultra-rare, even among the portion of the population with severe, early-onset obesity. These results are consistent with Rhythm's clinical epidemiology estimates of 100-500 POMC deficiency obesity and 500-2,000 LEPR deficiency obesity patients living in the U.S.

Additionally, Rhythm believes the sequencing yield in this cohort supports the Company's prior estimates of greater than 20,000 people living with high-impact heterozygous obesity of the *POMC, PCSK1* or *LEPR* genes in the U.S.

For the genetically-defined MC4R pathway indications that the Company has not previously included in prior clinical trials, the Company applied well-established functional and computational filtering processes to refine this yield and provide estimated U.S. prevalence[1]:

Indication	Estimated U.S. Prevalence
SRC1 deficiency obesity	>23,000
SH2B1 deficiency obesity	>24,000
MC4R deficiency obesity	>10,000

Syndromic conditions, such as SMS, BBS and Alström syndrome, are often clinically identified and confirmed by genetic testing. Rhythm estimates that there are greater than 2,400 people living with severe obesity and SMS in the U.S.

Update on Clinical Data from Phase 2 Basket Study in BBS and Alström Syndrome, and Community Building and Patient-Finding Efforts in these Two Indications

Rhythm provided an update on data from its Phase 2 Basket Study of setmelanotide in patients with BBS and Alström syndrome. As previously disclosed in January 2019, six of nine enrolled patients with BBS showed weight loss of greater than 10 percent on setmelanotide treatment. As of August 2019, all of these patients either continued to maintain, or increased, their weight loss following approximately two years of treatment, with a mean weight reduction of 22.2 percent. Additionally, five of six patients continued to show a substantial decrease in hunger from baseline.

In patients with Alström syndrome, the three patients on treatment at the Company's last update in November 2018 have continued on treatment. One of these patients has demonstrated 20 percent weight loss and a 25 percent reduction in hunger score at greater than one year. One patient has not lost weight but has demonstrated a 38 percent decrease in hunger and improved diabetes control at greater than one year, and the third patient achieved 6 percent weight loss without a change in hunger. All three patients plan to continue setmelanotide therapy in the long-term extension trial.

"Rhythm is working to build a community to better understand the substantial, long-term burden of rare genetic and syndromic disorders of obesity on the lives of patients and their families. Both BBS and Alström syndrome are typically diagnosed via clinical presentation, which requires an informed healthcare-provider community, capable of recognizing and managing the care of these patients," said Nithya Desikan, Chief Commercial Officer of Rhythm. "We believe we may have identified nearly one third of the estimated BBS and Alström patients living in the U.S., providing a foundation as we continue to enroll our pivotal Phase 3 trial in BBS and Alström syndrome, and begin to build the infrastructure to support the potential commercialization of setmelanotide in these indications."

Webcast Information:

The live audio webcast of today's R&D event can be accessed under "Events & Presentations" in the Investors & Media section of the Company's website at www.rhythmtx.com. A replay of the webcast will be available on the Rhythm website for 30 days following the event.

About Rhythm

Rhythm is a biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic disorders of obesity. The company recently announced positive topline results from pivotal Phase 3 clinical trials of setmelanotide, its MC4R agonist, in patients with POMC deficiency obesity and LEPR deficiency obesity, and Rhythm expects to

share the full data in forthcoming publications and medical meeting presentations. The company plans to complete its first rolling new drug application (NDA) submission to the U.S. Food and Drug Administration in the fourth quarter of 2019 or the first quarter of 2020. Rhythm is also evaluating setmelanotide in a pivotal Phase 3 study in patients with Bardet-Biedl syndrome and Alström syndrome, and expects to complete enrollment in the second half of 2019. The company is leveraging the Rhythm Engine -- comprised of its Phase 2 basket study, TEMPO Registry, GO-ID genotyping study and Uncovering Rare Obesity program -- to improve the understanding, diagnosis and potentially the treatment of rare genetic disorders of obesity. For healthcare professionals, visit www.UNcommonObesity.com for more information. For patients and caregivers, visit www.LEADforRareObesity.com for more information. The company is based in Boston, MA.

Forward-Looking Statements

This press release contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including statements regarding Rhythm's anticipated timing for enrollment of patients in clinical trials and submission of an NDA, its ongoing efforts related to patient identification, estimates of treatable patient populations, the timing of the release of results of clinical trials, the efficacy of setmelanotide in patients with POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl Syndrome, Alström Syndrome, POMC heterozygous deficiency obesity, or POMC epigenetic disorders, as well as new indications that we may pursue. 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, and expenses, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and quarterly reports on Form 10-Q and other reports we file 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] SRC1 and SH2B1 deficiency obesity epidemiology estimates include patients with high-impact loss-of-function variants, screened through three computational algorithms applied for newly-observed variants. These calculations assume a U.S. population of 327 million, of which 1.7% have early-onset, severe obesity (Hales et al in Jama – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); allele frequency based on Rhythm genetic sequencing (June 2019).

Rhythm PHARMACEUTICALS

Source: Rhythm Pharmaceuticals, Inc.