Mallinckrodt Announces New England Journal of Medicine Publication of Results from its Phase 3 CONFIRM Study of Terlipressin in Patients with Hepatorenal Syndrome Type 1 (HRS-1)

March 4, 2021

-- CONFIRM is the largest prospective study (n=300) conducted in patients with HRS-1, a life-threatening and acute form of advanced liver disease with high unmet needs and a poor prognosis --

DUBLIN, March 4, 2021 /PRNewswire/ -- Mallinckrodt plc, a global biopharmaceutical company, today announced publication of results from its pivotal Phase 3 CONFIRM study to assess the efficacy and safety of its investigational agent terlipressin in adults with hepatorenal syndrome type 1 (HRS-1). HRS-1 is an acute and life-threatening syndrome involving acute kidney failure in patients with cirrhosis,[1] and has a median survival time of approximately two weeks and greater than 80 percent mortality within three months if left untreated.[2,3] The study was posted online ahead of print publication in the *New England Journal of Medicine*.

Terlipressin is an investigational product and its safety and effectiveness have not yet been established by the U.S. Food and Drug Administration (FDA) or Health Canada.

As previously announced, the Phase 3 CONFIRM study met its primary endpoint of Verified HRS Reversal, which is defined as renal function improvement, avoidance of dialysis and short-term survival. The main objective of the CONFIRM study was to assess the efficacy and safety of terlipressin, together with albumin, versus placebo in adults in the U.S. and Canada with cirrhosis and HRS-1. The trial met three of the four pre-specified secondary endpoints of the study including HRS reversal, HRS reversal without renal replacement therapy (RRT) by Day 30 and HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup. The fourth pre-specified secondary endpoint of Verified HRS Reversal without HRS recurrence by Day 30 was 50 percent greater in the terlipressin group but did not reach statistical significance.[4] Initial results were announced during a late-breaking abstract presentation on November 11, 2019 at The Liver Meeting®, the annual meeting of the American Association for the Study of Liver Diseases (AASLD).

In another pre-specified endpoint, avoidance of RRT, terlipressin treated subjects (n=199) showed a significantly lower incidence during the treatment period and a lower incidence at all follow-up assessments through Day 90 versus patients with placebo (n=101).4 This is clinically significant because RRT can increase complications in HRS-1 due to the underlying cirrhosis (i.e. coagulopathy, low blood pressure).

"The durability of HRS reversal with terlipressin in CONFIRM persisted to Day 30 without the need for RRT. This is a clinically significant observation, as RRT poses many challenges for patients with advanced cirrhosis," said lead author **Florence Wong, MBBS, MD, FRACP, FRCPC, Hepatologist at Toronto General Hospital and Professor of Medicine at the University of Toronto**. "Results from CONFIRM provide critical information on a potential treatment option for HRS-1 and these data indicate that, if approved, terlipressin has the potential to reverse the course of HRS-1 in the appropriate patients and help the healthcare community better manage this critically ill and underserved patient population."

The incidence of adverse events (AEs) of any severity were similar in both groups (88.0 percent of the terlipressin group and 88.9 percent of the placebo group). The most commonly reported AEs in the overall study population were abdominal pain, nausea, diarrhea, hepatic encephalopathy and dyspnea. Serious AEs (SAEs) were reported in 65.0 percent (n=130) of the terlipressin group and 60.6 percent (n=60) of the placebo group. The most commonly reported SAEs included hepatobiliary disorders, respiratory disorders and gastrointestinal disorders.[4]

At present, there are no drug therapies approved for the treatment of HRS-1 in the U.S. or Canada.[5] HRS-1 is estimated to affect between 30,000 and 40,000 patients in the U.S. annually.[6,7]

In November 2020, Mallinckrodt announced it participated in an end of review meeting with the FDA to discuss the Complete Response Letter issued on September 11, 2020 for the Company's New Drug Application (NDA) for terlipressin. Based on recent discussions with the FDA, Mallinckrodt continues to explore a potential regulatory path forward regarding the NDA.

Terlipressin is approved in many countries outside the U.S. and Canada, where it has been a standard of care for decades in the treatment of patients with HRS-1.[8,9] Terlipressin, together with albumin, is currently the standard of care for HRS-1 in countries where it is approved and available.[10]

"The CONFIRM results provide meaningful insight into the management of HRS-1 in clinical practice, and we are pleased to be able to share these important data broadly with the healthcare community," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer**

at Mallinckrodt. "On behalf of Mallinckrodt, I would also like to once again thank all of the patients, caregivers and medical professionals whose contributions made this study possible."

About the Pivotal Phase 3 CONFIRM Study (multi-center, randomized, placebo-controlled, double-blind trial in the U.S. and Canada)[4]:

- The trial was designed to confirm efficacy and safety of terlipressin for the treatment of HRS-1.
- In the 35-month study period, 300 patients from the U.S. (89.0 percent) and Canada (11.0 percent) participated in the largest-ever prospective, multi-center, randomized, controlled clinical trial in HRS-1.
- Patients in the study were critically ill, as indicated by assessments of their liver and kidney function at the start of the trial. Patients in the trial had a mean Model for End-Stage Liver Disease (MELD) score of 33, a mean serum creatinine (SCr) level of 3.5 mg/dL and 61.0 percent were categorized as Child-Pugh Class C.
- Eligibility criteria included adults with liver cirrhosis and ascites with rapidly worsening renal function and no response to diuretic withdrawal or volume expansion with albumin.
- Subjects were randomized in a 2:1 ratio to receive terlipressin plus albumin (n=199) or placebo plus albumin (n=101).
- The primary endpoint of Verified HRS Reversal evaluated renal function improvement, avoidance of dialysis and short-term survival.

Find out more information about the CONFIRM trial here on the ClinicalTrials.gov website.

About Terlipressin
Terlipressin is a potent vasopressin analogue selective for V1 receptors being investigated for the treatment of HRS-1 in the U.S. and Canada. It is an investigational product in these countries as the safety and efficacy have not been established with, nor has approval been granted by, regulatory authorities in either country. Terlipressin is approved for use outside the U.S. and Canada.

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; analgesics and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS
This release includes forward-looking statements with regard to terlipressin, including with regard to interactions with regulators as well as its potential impact on patients. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

CONTACT

Media Inquiries
Caren Begun
Green Room Communications
201-396-8551
caren@greenroompr.com

Investor Relations
Daniel J. Speciale
Vice President, Finance and Investor Relations Officer
314-654-3638
daniel.speciale@mnk.com

References

[1] National Organization for Rare Disorders. Hepatorenal Syndrome. Available at: https://rarediseases.org/rare-diseases/hepatorenal-syndrome/. Accessed January 12, 2021.

[2] Colle I and Laterre PF. Hepatorenal syndrome: the clinical impact of vasoactive therapy. *Expert Review of Gastroenterology & Hepatology*. (2018) 12:2, 173-188, DOI: 10.1080/17474124.2018.1417034.

[3] Gines P, Sola E, Angeli P, et al. Hepatorenal syndrome. *Nature Reviews*. (2018) 4:23.

[4] Wong F, Pappas C, Curry M, et al. Terlipressin plus albumin for the treatment of hepatorenal syndrome type 1. *The New England Journal of Medicine*. 2020.

[5] Boyer TD, Medicis JJ, Pappas SC, et al. A randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin: the REVERSE trial design. Open Access Journal of Clinical Trials 2012:4. https://www.dovepress.com/a-randomized-placebo-controlled-double-blind-study-to-confirm-the-reve-peer-reviewed-article-OAJCT.

[6] C Pant, B S Jani, M Desai, A Deshpande, Prashant Pandya, Ryan Taylor, R Gilroy, M Olyaee. Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. *Journal of Investigative Medicine*. 2016;64:33–38.

[7] United States Census Bureau: Quick Facts. Available at: https://www.census.gov/quickfacts/fact/table/US/PST045218. Accessed January 12, 2021.

[8] De Franchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2005;43:167-176.

[9] Ioannou GN, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database of Systematic Reviews*. 2003;1. doi: 10.1002/14651858.CD002147.

[10] European Association for the Study of the Liver (EASL). Clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69(2):406-460.

View original content to download multimedia:http://www.prnewswire.com/news-releases/mallinckrodt-announces-new-england-journal-of-medicine-publication-of-results-from-its-phase-3-confirm-study-of-terlipressin-in-patients-with-hepatorenal-syndrome-type-1-hrs-1-301240196.html

SOURCE Mallinckrodt plc