# NEWSROOM

## News Release

# Mallinckrodt Presents Positive Phase 3 Results from its CONFIRM Study of Terlipressin in Patients with Hepatorenal Syndrome Type 1 (HRS-1) at The Liver Meeting® 2019

**-- Study showed a statistically significant number of patients on terlipressin achieved the primary endpoint of Verified HRS Reversal vs placebo --**

**-- 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 --**

**-- The CONFIRM abstract was selected by the AASLD Selection Committee for the "Best of the Liver Meeting" educational program in the portal hypertension / cirrhosis category --**

STAINES-UPON-THAMES, United Kingdom, Nov. 11, 2019 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced 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 people with cirrhosis.[1] Results were reported during a late-breaking abstract presentation today at The Liver Meeting® 2019, the annual meeting of the American Association for the Study of Liver Diseases (AASLD), in Boston. The CONFIRM abstract was also selected by AASLD for inclusion in its prestigious "Best of the Liver Meeting" educational program in the portal hypertension/cirrhosis category.

In the 35-month study period, 300 patients from the U.S. (89 percent) and Canada (11 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 percent were categorized as Child-Pugh Class C.[2]

The study met its primary endpoint of Verified HRS Reversal (VHRSR), which is defined as renal function improvement, avoidance of dialysis and short-term survival. 29.1 percent (58/199) of patients administered terlipressin plus albumin achieved Verified HRS Reversal versus 15.8 percent (16/101) on placebo plus albumin

(p=0.012). In order to achieve Verified HRS Reversal, patients had to have two consecutive SCr values ≤1.5 mg/dL, at least two hours apart by day 14 or hospital discharge, and be alive without intervening renal replacement therapy (RRT) for at least 10 days following discharge or treatment.[2]

"HRS-1 is a rapidly progressing and often fatal disease that is extremely difficult to diagnose and treat, and many patients don't live beyond a few weeks without treatment. The results from the CONFIRM trial are very encouraging, and show terlipressin, if approved, has the potential to reverse the course of HRS-1 as measured by renal function improvement, avoidance of dialysis and short-term survival," said presenting author **Florence Wong, MBBS, MD, FRACP, FRCPC, hepatologist at Toronto General Hospital, and professor of Medicine at the University of Toronto**. "These results provide important information that may help the healthcare community better manage this critically ill and underserved patient population."

HRS-1 has a median survival time of less than two weeks and greater than 80 percent mortality within three months if left untreated.[3,4] At present, there are no approved drug therapies for 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] Terlipressin is an investigational product and its safety and effectiveness have not yet been established by the U.S. FDA or Health Canada. The company plans to submit a New Drug Application to the U.S. Food and Drug Administration (FDA) in the first half of 2020.

"We are grateful to all the patients and investigators who participated in the CONFIRM trial and greatly encouraged by the positive results, which demonstrated that terlipressin may have a potential impact on the progressively worsening kidney function that is the hallmark of HRS-1," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt**. "Today marks the culmination of a long clinical development journey led by our passionate, dedicated clinical development team. The results from this largest-ever prospective phase 3 clinical trial in HRS-1 provide meaningful insight into the management of HRS-1 in clinical practice."

**CONFIRM Study Key Findings[2]**

- The study met its primary endpoint of **Verified HRS Reversal**, defined as two consecutive SCr values ≤1.5 mg/dL, at least two hours apart by day 14 or discharge, with subjects alive without RRT for at least 10 days after the second SCr ≤1.5 mg/dL.
    - 29.1 percent (n=58) of patients treated with terlipressin plus albumin compared to 15.8 percent (n=16) of patients treated with placebo plus albumin (p=0.012) achieved Verified HRS Reversal.
- The four pre-specified secondary endpoints of the study were:
    - **HRS reversal:** 36.2 percent (n=72) of patients in the terlipressin group demonstrated HRS reversal, defined as the percentage of participants with a SCr value no more than 1.5 mg/dL by day 14 or discharge versus 16.8 percent (n=17) on placebo (p<0.001).
    - **Durability of/maintaining HRS reversal:** 31.7 percent of patients receiving terlipressin (n=63) maintained HRS reversal without RRT/dialysis up to day 30 versus 15.8 percent (n=16) in the placebo group (P<0.003).

- **HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup:** 33.3 percent (28/84) of patients with SIRS in the terlipressin arm achieved Verified HRS reversal versus 6.3 percent (3/48) in the placebo arm (p<0.001).
- **Verified HRS Reversal without HRS recurrence by day 30:** 24.1 percent (n=48) of patients on terlipressin and 15.8 percent (n=16) of patients in the placebo group (p=0.092) achieved Verified HRS Reversal without recurrence by day 30.

- Adverse events (AEs) were similar in both groups. Serious AEs were reported in 65 percent (n=130) of subjects in the terlipressin group and 60.6 percent (n=60) in the placebo group. The most commonly reported serious AEs included respiratory failure, which occurred in 10 percent of the terlipressin group and 3 percent of the placebo group; and abdominal pain, which occurred in 5 percent of the terlipressin group and 1 percent of the placebo group. The most commonly reported AEs included abdominal pain, which occurred in 19.5 percent of the terlipressin group and 6.1 percent of the placebo group; and nausea, which occurred in 16 percent of the terlipressin group and 10.1 percent of the placebo group. Ischemia-associated AEs occurred in 4.5 percent of the terlipressin group and 0 percent in the placebo group. No new or unexpected AEs were reported.

**About the Pivotal Phase 3 CONFIRM Study (multi-center, randomized, placebo-controlled, double-blind trial in the U.S. and Canada):**[2]

- The trial was designed to confirm efficacy and safety of terlipressin for the treatment of HRS-1
- CONFIRM is the largest prospective trial ever conducted (n=300) in HRS-1 patients
- 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.

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**CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS**

This release includes forward-looking statements with regard to terlipressin and the study described in this release, including 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**

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

**For Financial/Dailies Media Inquiries**
Daniel Yunger
Kekst CNC
212-521-4879
mallinckrodt@kekstcnc.com

**Investor Relations**
Daniel J. Speciale, CPA
Vice President, Investor Relations and IRO

314-654-3638
daniel.speciale@mnk.com



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