CLINICAL STUDY PROTOCOL

A Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study To Confirm Efficacy And Safety Of Terlipressin In Subjects With Hepatorenal Syndrome Type 1

(The CONFIRM Study – Incorporating Amendments 1, 2 and 3)

Protocol Number:	MNK19013058
Study Drug:	Terlipressin (Terlivaz®)
Development Phase:	Phase 3
IND Number:	68,582
Original Protocol Date:	01 March 2016
Amendment #1 Date:	09 May 2016
Amendment #2 Date:	16 December 2016
Amendment #3 Date:	26 September 2018
Sponsor:	Mallinckrodt Pharmaceuticals Clinical Research and Development 1425 US Route 206 Bedminster, NJ, 07921 United States of America

EMERGENCY CONTACT INFORMATION

Role in Study	Name	Address and Telephone Number
Clinical Study Manager	[redacted]	1425 US Route 206 Bedminster, NJ, 07921 Office: [redacted]
Clinical Technical Lead	[redacted] MD	1425 US Route 206 Bedminster, NJ, 07921 Office: [redacted]
Medical Hotline		The hotline number will be provided in the study manual.

[Pages 2-19 and 27-108 Redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Subjects with Hepatorenal Type 1 Syndrome (The CONFIRM Study)" and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), the ethical principles stated in the latest version of the Declaration of Helsinki, and the applicable local and international regulations, whichever provide the greater protection of the individual.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor, Mallinckrodt Inc.

Investigator's Signature	Date (Day/Month/Year)

Sponsor Statement

This study protocol was subject to critical review and has been approved by the following sponsor representative.

[redacted], MD

02-10-2018
Date (Day/Month/Year)

[redacted]
Mallinckrodt Inc
1425 US Route 206
Bedminster, NJ, 07921
Office: [redacted]

2 Synopsis

Name of Sponsor/Company: Mallinckrodt Pharmaceuticals.
Name of Investigational Product: Terlivaz®.
Name of Active Ingredient: Terlipressin.
Title of Study: A Multi-Center, Randomized, Placebo-Controlled Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Subjects With Hepatorenal Syndrome Type 1 (The CONFIRM Study)
Study Centers: Approximately 70 sites in the United States of America and Canada.
Phase of Development: Phase 3.
Objectives: To confirm the efficacy and safety of intravenous terlipressin vs placebo in the treatment of adult subjects with hepatorenal syndrome (HRS) Type 1 receiving standard of care albumin therapy.
Methodology: Randomized, placebo-controlled, double-blind, multi-center study. 2:1 randomization to terlipressin 1 mg intravenously (IV) every 6 hours vs placebo.
Number of Subjects (Planned): 300 subjects.
Diagnosis and Main Inclusion/Exclusion Criteria: Adult subjects with cirrhosis, ascites, and a diagnosis of HRS Type 1 based on the 2007 and 2015 updated International Ascites Club (IAC) diagnostic criteria. **Inclusion Criteria:** 1. Written informed consent by subject or legally authorized representative. 2. At least 18 years of age. 3. Cirrhosis and ascites. 4. Rapidly progressive worsening in renal function to a serum creatinine (SCr) at least 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks. 5. No sustained improvement in renal function (less than 20% decrease in SCr and SCr at least 2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin. **Exclusion Criteria:** 1. Serum creatinine level greater than 7.0 mg/dL. 2. At least 1 event of large volume paracentesis (LVP) at least 4 L within 2 days of randomization. 3. Sepsis and/or uncontrolled bacterial infection (eg, persisting bacteremia, persisting ascitic fluid leucocytosis, fever, increasing leucocytosis with vasomotor instability). 4. Less than 2 days anti-infective therapy for documented or suspected infection. 5. Shock. 6. Current or recent (within 4 weeks) treatment with or exposure to nephrotoxic agents: eg, aminoglycosides, amphotericin, cyclosporine A, cisplatin, nonsteroidal anti-inflammatory drugs (NSAIDs: eg, ibuprofen, naproxen, diclofenac), significant exposure to radiographic contrast agents (large doses or multiple injections of iodinated contrast media; eg, during coronary or abdominal angiogram). 7. Estimated life expectancy of less than 3 days. 8. Superimposed acute liver injury due to drugs (eg, acetaminophen), dietary supplements, herbal preparations, viral hepatitis, or toxins (eg, *Amanita* toxin with mushroom poisoning carbon tetrachloride), with the exception of acute alcoholic hepatitis. 9. Proteinuria greater than 500 mg/day. 10. Evidence of obstructive uropathy or parenchymal renal disease on ultrasound or other imaging. 11. Tubular epithelial casts, heme granular casts, hematuria or microhematuria (greater than 50 red blood cells

per high power field in the absence of recent catheterization) on urinalysis.

Note: Urine sediment examination is required to exclude presence of heme granular casts and other clinically significant casts.

12. Subjects known to be pregnant; all women of child-bearing age and potential must have a negative pregnancy test.
13. Severe cardiovascular disease, including, but not limited to, unstable angina, pulmonary edema, congestive heart failure requiring increasing doses of drug therapy, or persisting symptomatic peripheral vascular disease, myocardial infarction or stable chronic angina within the past 12 months, or any other cardiovascular disease judged by the investigator to be severe.
14. Current or recent (within 4 weeks) renal replacement therapy (RRT).
15. Participation in other clinical research involving investigational medicinal products within 30 days of randomization.
16. Transjugular intrahepatic portosystemic shunt (TIPS) within 30 days of randomization.
17. Use of vasopressors (eg, norepinephrine, epinephrine or vasopressin dopamine or other vasopressors) of at least 3 consecutive days within the prior 14-day screening period. Patients receiving a vasopressor other than midodrine within 24 hours of qualifying SCr are excluded, ie, a 24-h washout is required prior to enrollment.

Note: Patients receiving midodrine and octreotide may be enrolled. Midodrine and octreotide treatment must be stopped prior to randomization.

18. Known allergy or sensitivity to terlipressin or another component of the study treatment.

Investigational Product, Dosage and Mode of Administration:

[redacted] terlipressin acetate [redacted] reconstituted with 5 mL of sterile 0.9% sodium chloride solution.

Reference Therapy, Dosage and Mode of Administration:

Matching placebo [redacted] identical in appearance to terlipressin for injection [redacted]

Treatment Discontinuation:

Treatment should be continued until 24 hours after a second consecutive SCr value no more than 1.5 mg/dL has been obtained, OR up to a maximum of 14 days [redacted]

If on Day 4 [redacted] SCr is at or above baseline value, study drug should be discontinued.

Treatment must be discontinued when the subject is to undergo RRT, liver transplantation, TIPS or vasopressor

therapy.

Dosing must be permanently discontinued if an event of cardiac ischemia or mesenteric ischemia occurs.

Retreatment:

If judged by the investigator to be potentially beneficial, subjects who demonstrate at least a partial response during the initial treatment course [redacted] may be retreated with initially assigned blinded study drug for a maximum of 14 days (from the beginning of the retreatment, treatment and study procedures will be identical to the initial therapy). To qualify for retreatment the subject must again meet the study inclusion/exclusion criteria and the sponsor must be contacted prior to initiation of retreatment. Retreatment may occur within 90 days of the subject's first dose of study drug. Subjects will not be re-randomized or re-stratified for the retreatment cycle.

Duration of Treatment:

The active treatment period will be 14 days (exception: 15 days as described above), allowing 1 retreatment cycle. Subjects will have a scheduled follow-up visit for Day 30 (±10), and will be contacted by phone for Day 60 (±14), and Day 90 (±14).

Criteria for Evaluation:

Primary Efficacy Endpoint:

Incidence of verified HRS reversal, defined as the percentage of subjects with 2 consecutive SCr values no more than 1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge (on treatment defined as up to 24 hours after the final dose of study drug). [redacted]

Secondary Efficacy Endpoints:

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL by Day 14 or discharge [redacted]
- Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. [redacted]
- Incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup. [redacted]
- Incidence of verified HRS reversal without HRS recurrence by Day 30. [redacted]

[redacted]

Safety:

Safety assessments will include the following:

- Non-serious adverse events up to 7 days after end of treatment.
- Serious adverse events up to 30 days after end of treatment.
- General safety profile, including physical examinations, vital signs and laboratory tests.
- Mortality up to 90 days after the first dose of study drug.

Statistical Methods:

Primary Efficacy Analysis:

- The primary efficacy variable of verified HRS reversal is defined as the percentage of subjects with 2 consecutive SCr values no more than 1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge (on treatment defined as up to 24 hours after the final dose of study drug). [redacted] Verified HRS reversal will be summarized by treatment group and analyzed using a Z score based on the upper alpha boundary values for the interim and final analyses. The upper alpha boundary value for the interim analysis is 2.79651. At the interim analysis, if the Z score is greater than 2.79651 then the study will stop

for early success. If the Z score is no more than 2.79651 then the study will continue to the final analysis. The final analysis will be successful if the Z score is greater than 1.97743.

Secondary Efficacy Analyses:

A Hochberg procedure for multiple testing and the alpha level corresponding to the Z score of the primary efficacy analysis will be used for testing the secondary efficacy analyses at either the interim analysis or the final analysis.

Sample Size:

[redacted]

With a 2:1 randomization of terlipressin to placebo and an interim analysis after 50% of the subjects have completed Day 14 or Discharge, 300 subjects will provide 89.76% power to detect a statistically significant difference between the groups.

Interim Analysis:

An interim analysis will be performed after 50% of the subjects have completed Day 14 or discharge, [redacted]