Official Title: 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)

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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

SUMMARY OF CHANGES FROM AMENDMENT 2 TO AMENDMENT 3

DATED 26 SEPTEMBER 2018

This protocol amendment was required in order to address FDA comments and recommendations from a meeting on 13 September 2018.

A sentence was added as follows: *SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.*

This sentence was added to the following sections:

1. Protocol Synopsis, Criteria for Evaluation, Primary Efficacy Endpoint (pg 25).
2. Protocol Synopsis, Criteria for Evaluation, Secondary Efficacy Endpoints, Fourth Bullet Point (pp 25-26).
3. Protocol Synopsis, Statistical Methods, Primary Efficacy Analysis (pg 26).
4. Primary Efficacy Variables, Section 6.1.1.
5. Secondary Efficacy Variables, Fourth Bullet Point, Section 6.1.2.
6. Primary Efficacy Variable, First Paragraph, Section 13.6.1.
7. Secondary Efficacy Variable, Last Paragraph, Section 13.6.2.
8. Primary Efficacy Analysis, First Paragraph, Section 15.3.6.1.
9. Secondary Efficacy Analyses, Last Paragraph, Section 15.3.6.2.

The sponsor's address was updated on the title page, pg 20 and pg 22. The Mallinckrodt clinical study manager name was updated on pg 20. ICH name was updated.

SUMMARY OF CHANGES FROM AMENDMENT 1 TO AMENDMENT 2

DATED 16 DECEMBER 2016

This protocol amendment was required in order to address FDA comments and recommendations from a letter dated 14 October 2016.

1. Physical Examinations: Physical examinations have been changed (Table 13–1, Schedule of Assessments and Section 13.3.1) to add abbreviated physical examinations every day during the 14-day active study period in addition to the general physical assessment examinations conducted at baseline and the 30-day post-treatment follow-up.

2. Qualifying Serum Creatinine For Subjects Taking Vasopressors at Baseline: The protocol text (Section 8.3, Section 13.2.2, Section 13.6, and Appendix A) was modified to clarify that the qualifying serum creatinine for subjects on vasopressors will be taken after vasopressor washout.

3. Definition of HRS Recurrence: The endpoint definition of HRS recurrence was revised (Section 10.5) to state all parameters explicitly.

4. Sensitivity Analyses: The text (Section 15.3.6.3) regarding sensitivity analyses was revised to specify sensitivity analyses related to the assumption that if the investigator cannot exclude a recurrence of HRS Type 1, the subject will be considered to have a recurrence.

5. Withdrawal By Subject: The text (Section 8.5) was revised to specify that a reason will be recorded.

6. Death of Subject: The text (Section 14.3.1) was revised to specify the collection and recording of the investigator-reported immediate cause of death on the appropriate eCRF page.

7. Ischemic Abdominal, Cardiac and Respiratory Adverse Events: The text (Section 14.2) was revised to specify that all necessary data are collected and recorded to determine whether an ischemic abdominal event, ischemic cardiac event, or a bronchospasm-related respiratory event has occurred.

8. Title Page and Headers: The text of every page was revised to indicate "Incorporating Amendments 1 and 2" and an Amendment 2 revision date was added to the title page.

9. Any additional format, spelling, or grammatical changes were made as needed.

SUMMARY OF CHANGES FROM THE ORIGINAL PROTOCOL
TO AMENDMENT 1

DATED 09 MAY 2016

This protocol amendment was required in order to address FDA recommendations from the Special Protocol Assessment (SPA) agreement letter dated 21 April 2016. The amendment incorporates FDA comments as outlined in the SPA agreement letter and agreements as outlined in an IND communication of 15 April 2016.

For the changes noted below, deletions are indicated by strikethrough font and additions by italics.

1. Protocol Synopsis, Primary Efficacy Endpoint: The primary efficacy analysis timing after the final dose of study drug was changed from 72 hours to 24 hours as follows:

> *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).*

2. Protocol Synopsis, Secondary Efficacy Endpoint: The definitions of HRS reversal and RRT were clarified and provided in the protocol synopsis as follows:

- Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques.

- Incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup, defined as the percentage of SIRS subjects with HRS reversal. *HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while*

on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).

- Incidence of verified HRS reversal without HRS recurrence by Day 30. HRS Type 1 recurrence is defined in Section 10.5. Incidence 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 up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis.

3. Protocol Synopsis, [redacted]

[redacted]

4. Protocol Synopsis, Treatment Discontinuation, first sentence, was modified as follows:

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 (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14).

5. Protocol Synopsis, Statistical Methods:

A. The first sentence in the 'Primary Efficacy Analyses' subsection was modified as follows:

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).

B. The 'Secondary Efficacy Analyses' subsection was modified as follows:

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.

C. The 'Sample Size' subsection was modified as follows:

[redacted]

~~PROC SEQDESIGN in SAS (SAS® software version 9.2 or higher) was used for the sample size calculation.~~ 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 ~~90~~89.76% power to detect a statistically significant difference between the groups.

6. Section 6.1.1 was modified as follows:

   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).*

7. Section 8.1 was modified as follows:

   Subjects with a baseline SCr level greater than 7.0 mg/dL will be excluded from the study.

   ~~In this study, the threshold for the upper cut of SCr will be set to exclude subjects with SCr > 6 mg/dL.~~ *The threshold for upper cut-off of SCr in entry criteria is derived from the results of previous NDA studies. In OT-0401, none of the subjects with a baseline SCr level greater than 7.0 mg/dL achieved HRS reversal. Subjects will be stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL).*

   ~~where, across individual studies as well as in the pooled analysis, subjects with SCr of ≤ 6 mg/dL have shown a much greater likelihood of achieving HRS reversal than subjects with SCr > 6 mg/dL. Pooling the OT-0401 and REVERSE studies resulted in 11.1% (1/9) of subjects with SCr > 6 mg/dL achieving HRS reversal and 37.4% (49/131) of subjects with SCr ≤ 6 mg/dL achieving HRS reversal. The aim of lowering the upper cut-off is to minimize exposure to terlipressin in subjects with high SCr who may not receive as much benefit to therapy but still be exposed to the risks of the therapy.~~ *Subjects will be stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL).*

   Qualifying SCr is a prognostic factor for survival and HRS reversal. Excluding subjects with a baseline SCr of greater than ~~6~~ 7 mg/dL and LVP at least 4 L within 2 days prior to

randomization (both are exclusion criteria for this study), 3.4 mg/dL (N = 253) was the median baseline SCr of subjects enrolled in the OT-0401 and REVERSE studies combined.

8. Section 8.4, Exclusion Criteria, was modified (and in Synopsis) as follows:

   #9. The footnote to this criterion was moved under exclusion #11.

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

   #11. A footnote was added :

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

   #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.

   #17. ~~Ongoing use~~Use of vasopressors (eg, ~~midodrine~~norepinephrine, epinephrine *or vasopressin, dopamine or other vasopressors)* ~~or octreotide~~ of at least 3 consecutive days within 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.~~*doses will require a washout of 8 hours before randomization.~~

9. Section 10.3.1 was modified as follows:

   Blinded terlipressin or placebo will be administered intravenously as a bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (± 30 minutes). *After study drug administration the line should be flushed with saline.*

10. Section 10.4 was modified as follows:

- Treatment should be continued until 24 hours after ~~a~~ *2 consecutive* SCr value*s* no more than 1.5 mg/dL hav~~es~~ been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14).

11. Section 10.5 was modified as follows:

Any subject with a SCr value of at least 2.25 mg/dL after achieving verified HRS reversal, but prior to transplant/discharge/Day 14, will be assessed for HRS Type 1 recurrence. ~~HRS Type 1 recurrence is another episode of HRS Type 1 as per the protocol inclusion/exclusion criteria.~~ *HRS recurrence by Day 30 is defined as another episode of HRS Type 1, by Day 30, after achieving verified HRS reversal, characterized by rapidly progressive worsening in renal function to a SCr at least 2.25 mg/dL, without 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, and meeting all other inclusion and exclusion criteria defining the initial diagnosis of HRS Type 1.* The investigator will determine whether the subject has had a recurrence of HRS Type 1. If the investigator cannot exclude a recurrence of HRS Type 1, then the subject will be considered to have HRS Type 1 recurrence.

HRS Type 1 recurrence will be monitored as follows: Recurrence of HRS Type 1 during the follow-up period (after discharge or Day 14) will be assessed based upon the investigator's opinion and serious AE data collected up to 30 days after end of treatment. Following the initial hospital discharge, all re-hospitalizations within 30 days after end of treatment (except for planned hospital admissions or procedures as described in the protocol) are to be recorded as an SAE. Re-hospitalizations will require an investigator assessment and opinion regarding possible recurrence of HRS Type 1. *All available relevant medical records, MedWatch forms, discharge summaries or other relevant source documents should be requested and reviewed for all SAEs, including all hospitalizations, until 30 days after discontinuation of study drug.*

12. Section 11.3 was modified as follows:

Study drug should be stored in a secure location at 2ºC to 8ºC until reconstitution and can be stored up to ~~24~~ 48 hours at refrigerated storage conditions (2ºC to 8ºC) once reconstituted with sterile 0.9% NaCl solution~~provided~~.

13. Table 13–1 (Schedule of Assessments) was revised as follows:

A. The 'Discharge' column heading was changed to read: *Day 14[b] or* Discharge, *whichever occurs first*.

B. A new table row was added requiring a venous blood lactate level to be taken at baseline.

C. A new table row was added requiring the recording of all post-treatment paracentesis events.

D. Footnote 'h' was revised as follows:

[h]Medical history will include assessment of multi-organ dysfunction at baseline (refer to Section 13.3.5 and the Site/Investigator Study Manual for additional details).

E. Footnote 'l' was revised as follows:

[l]Treatment should be continued until 24 hours after ~~a~~ *2 consecutive* SCr value*s* no more than 1.5 mg/dL ha*ve*~~s~~ been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14, when the Day 14 assessments will be performed on Day 15). Window is (± 30 minutes).

F. The former footnote 'n' was deleted and remaining footnotes were re-lettered. The new footnote 'n' incorporates FDA comments.

G. The new footnote 'n' (former footnote 'o') was revised (additions in italics) as follows:

[n]A blood sample for measurement of SCr must be drawn before discharge. The second verifying sample of SCr no more than 1.5 mg/dL must be taken at least 2 hours apart and must be consecutive.

H. The new footnote 's' was revised as follows:

[s]All subjects will be ~~contacted by telephone~~ required to come back for ~~for follow up on~~ Day 30 (± 10) *visit and will be contacted by phone for Day* 60 (± 14), and Day 90 (± 14) follow up to assess survival, RRT, TIPS and liver transplant status. Study days will be counted from first day of study drug administration (or from randomization for those subjects who do

not receive study drug). All information regarding RRT, TIPS and liver transplant must be collected.

I. The new footnote 't' was revised as follows:

[t]For the Day 30 follow-up visit, all subjects are required to provide a blood sample for SCr ~~and BUN~~. The site staff must also collect an updated medical history, vital signs, concomitant medications, SAE assessment, *paracentesis events,* RRT, and HRS recurrence.

14. Section 13.2.3.2, first paragraph, was revised as follows:

Treatment should be continued until 24 hours after ~~a~~ *2 consecutive* SCr value*s* no more than 1.5 mg/dL ha*ve*~~s~~ been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14, when the Day 14 assessments will be performed on Day 15).

15. Section 13.2.4, second paragraph, was revised as follows:

All subjects *will have a follow up visit* ~~or be contacted by telephone for follow up~~ on Day 30 (± 10), *while Day 60* (± 14), and *Day* 90 (± 14) *follow up can be done via telephone* to assess survival, RRT, TIPS, and liver transplant status. *Study days will be counted from first day of study drug administration (or from randomization for those subjects who do not receive study drug). In addition, during the Day 30 follow-up, a* blood sample will be obtained to assess ~~serium creatine~~serum creatinine. A physical examination, ~~will be performed, and~~ updated ~~data on~~ medical history, vital signs, concomitant medications, and SAE assessments will also be collected. ~~On Days 60 and 90 (±14 days), the follow up will be completed via telephone to assess survival, RRT, TIPS, and liver transplant status.~~

In the same section, the third paragraph is deleted:

~~All subjects will be contacted by telephone for follow up on Days 30 (± 10), 60 (± 14), and 90 (± 14) follow up can be done via telephone to assess survival, RRT, TIPS, and liver transplant status. Study days will be counted from first day of study drug administration (or from randomization for those subjects who do not receive study drug). In addition, during the Day 30 follow-up, a physical examination will be performed, and updated data on medical history, vital signs, concomitant medications, and SAE assessments will be collected.~~

16. Section 13.2.4.1 was modified as follows:

All subjects will be required to provide a blood sample at Day 30 (± 10 days) for analysis of SCr ~~and BUN~~. This blood sample can be drawn during the Day 30 visit or by a visiting nurse if the subject is unable to return to the study site during the Day 30 follow-up window. *Every effort will be made to collect a blood sample at Day 30 for all possible subjects. No imputation will be made for missing values.*

17. Section 13.3.1, 3rd paragraph, was modified as follows:

The investigator may perform additional unscheduled examinations to manage or evaluate a suspected AE as clinically necessary. The timing and scope of additional unscheduled examinations should be determined by the nature and severity of the AE being evaluated. In the case of suspected cardiac, intestinal or other ischemia, examination of the subject by a physician should be completed on an emergency basis (generally within 15-30 minutes). For suspected cardiac ischemia, examination should include assessment of vital signs, cardiac and pulmonary auscultation, and evaluation of jugular venous pressure by clinical examination and other components as determined by the physician's clinical judgment. *For suspected cardiac ischemia, site must performed an ECG and cardiac enzymes (high sensitivity troponin) at the time of assessment and 3 hours later.* Subjects with suspected intestinal ischemia should undergo careful examination of the abdomen to evaluate for the presence of diffuse or focal tenderness, rebound, or acute abdomen with diffuse rigidity. *For suspected intestinal ischemia, venous (blood) lactate levels must be drawn and compared to baseline levels. Further investigations should be carried out based on clinical practice.* All subjects ~~with suspected ischemia~~ should have evaluation of the skin of the trunk and extremities for mottling, cyanosis, blanching or pallor.

18. Section 13.3.2 was modified as follows:

A 12-lead electrocardiogram (ECG) will be performed at baseline. Clinically relevant abnormalities found will be reported on the medical history page. The investigator may perform additional unscheduled examinations to manage or evaluate a suspected AE as clinically necessary. Clinically relevant abnormalities found upon subsequent ECGs will be reported and analyzed as AEs ~~and on ECG CRF~~. *The dates of all subsequent ECGs will be reported on the ECG eCRF.*

19. Section 13.5.1 was modified as follows:

The laboratory tests specified in this section will be performed in the laboratory at the investigational site. All local laboratories must use the isotope dilution mass spectroscopy method for the serum creatinine assay. All efforts should be made to take the blood sample from a clean new venous site, or the second option could be a central venous line to collect the blood specimen. Site personnel should not draw the blood sample from an existing peripheral venous access site or a line used for IV fluid administration. *See Site/Investigator's Study Manual for additional details regarding blood drawing technique.*

20. Section 13.5.1.1 (2nd bullet) was modified as follows:

- Blood urea nitrogen (BUN) (not collected at 30-day follow-up).

21. Section 13.6.1 was modified as follows:

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 ~~72~~*24* hours after the final dose of study drug). Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from primary end point analysis.

SCr data for the primary end point will be collected at least daily until discharge or Day 14. The analysis will be based on ITT population. Treatment should be continued until 24 hours after a *second confirmatory* SCr value no more than 1.5 mg/dL has been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14). The date and time of the first observed SCr value of no more than 1.5 mg/dL (HRS reversal) will be used for calculating the time window for the verifying SCr value. The ~~first~~ *next (consecutive)* SCr value of no more than 1.5 mg/dL *must occur*~~ring~~ during the time window *in order to have a verified HRS reversal* ~~for verification will be selected as the second and verifying value~~. *The date RRT is instituted for the first time will be used to determine if a subject underwent RRT by Day 30.*

22. Section 13.6.2, Secondary Efficacy Variables, was modified as follows:

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL *while on treatment* by Day 14 or discharge (SCr

values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).

- Durability of HRS reversal: the percentage of subjects with HRS reversal without RRT to Day 30. *HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques. The date RRT is instituted for the first time will be used to determine if a subject underwent RRT by Day 30.*

- Incidence of HRS reversal in the SIRS subgroup: the percentage of SIRS subjects with HRS reversal. ~~SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded.~~ *HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).* The SIRS subgroup is defined as any subject with at least 2 of the following criteria: WBC less than 4,000 or greater than 12,000 cells/µL; heart rate greater than 90 bpm; temperature greater than 38°C or less than 36°C; respiratory rate greater than 20/min; HCO_3 less than 21 mmol/L; the latter criterion represents an approximation of the SIRS criterion $PaCO_2$ of less than 32 mm Hg, derived from the observed HCO_3 in subjects with HRS in whom a $PaCO_2$ value was available (from the TAHRS study) and the calculated HCO_3 in subjects with decompensated liver disease and $PaCO_2$ of less than 32 mm Hg.

- *Incidence of verified HRS reversal without* HRS recurrence by Day 30 ~~HRS Type 1 recurrence is another episode of HRS Type 1 as per the protocol inclusion/exclusion criteria~~ is *defined in Section 10.5. 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 up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis.*

23. [redacted]

24. Section 15.3.1, Sample Size Calculation, was revised as follows:

[redacted]

Table 15-1: Sample Size Estimates

[redacted]

Based on REVERSE, subjects without a known event of pre-enrollment LVP at least 4 L within 2 days of randomization and OT-0401 subjects with baseline SCr no more than 7 mg/dL. SCr values were included while the subjects were on treatment, up to ~~72~~ *24* hours after the final dose of study drug. SCr values were excluded after RRT and transplant. If a subject died within 10 days after the reversal, then the subject did not have a reversal. If a subject has an RRT by the 30-day follow-up visit, then the subject did not have a reversal. *Three REVERSE terlipressin subjects who achieved a reversal after the 24 hour window were counted as reversals because they would have continued on study drug based on the CONFIRM trial design through the reversal.*

~~PROC SEQDESIGN in SAS (SAS® software version 9.2 or higher) was used for the sample size calculation. The SAS code and SAS output are in Section 23.~~ 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 ~~90~~ *89.76*% power to detect a statistically significant difference between the groups, 200 subjects in the terlipressin group and 100 subjects in the placebo group.

25. Section 15.3.6.1, Primary Efficacy Analysis, 1st paragraph, was revised as follows:

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 ~~72~~*224* hours after the final dose of study drug). Subject must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from primary end point analysis.

26. Table 15–2 (Title only) was revised as follows:

Table 15-2: Potential Scenarios for Success at the Interim Analysis with a Placebo Rate of Approximately ~~13~~ *12.5*%

27. Section 15.3.6.2, Secondary Efficacy Analysis was revised as follows:

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.

If the interim analysis for the primary endpoint is successful then the secondary efficacy analyses will be tested against a corresponding p-value of 0.005166 for a Z score of 2.79651. The p-values from the 4 secondary efficacy analyses will be ordered from largest to smallest and will be compared as in the table below:

Table 15-3: Multiple Testing for the Interim Analysis of the Secondary Efficacy Analyses

p-value Ordering	α Comparator	If p-value less than α then:	If p-value at least α then:
Largest p-value	0.005166 =0.005166/(4-4+1)	All 4 analyses are significant	Test the second largest p-value
Second largest p-value	0.002583 =0.005166/(4-3+1)	The remaining 3 analyses are significant	Test the third largest p-value
Third largest p-value	0.001722 =0.005166/(4-2+1)	The remaining 2 analyses are significant	Test the smallest p-value
Smallest p-value	0.001292 =0.005166/(4-1+1)	This analysis is significant	No analyses are significant

If the interim analysis for the primary endpoint is not successful then the study will continue onto the final analysis. If the primary efficacy analysis is successful, then the secondary efficacy analyses will be tested against a corresponding p-value of 0.047993 for a Z score of 1.97743, as shown in the table below:

Table 15-4: Multiple Testing for the Final Analysis of the Secondary Efficacy Analyses

p-value Ordering	α Comparator	If p-value less than α then:	If p-value at least α then:
Largest p-value	0.047993 =0.047993/(4-4+1)	All 4 analyses are significant	Test the second largest p-value
Second largest p-value	0.023997 =0. 047993/(4-3+1)	The remaining 3 analyses are significant	Test the third largest p-value
Third largest p-value	0.015998 =0. 047993/(4-2+1)	The remaining 2 analyses are significant	Test the smallest p-value
Smallest p-value	0.011998 =0. 047993/(4-1+1)	This analysis is significant	No analyses are significant

~~If the primary endpoint is found significant, the pre-specified secondary efficacy endpoints will be analyzed in a sequential manner at the 0.05 level of significance. Testing will stop if a secondary endpoint is not significant.~~ The following are the secondary endpoints:

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL, while on treatment up to ~~72~~ *24* hours after the final dose of study drug, by Day 14 or discharge. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded. HRS reversal will be summarized by treatment group and analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and pre-enrollment LVP (at least one single event of at least 4 L or less than 4 L within 3 to 14 days prior to randomization). If the proportion of subjects with HRS reversal is small (expected cell counts less than 5), an unstratified Chi-square test will be used instead of the CMH test. If the number of events per cell is still less than 5, then a Fisher's Exact test will be used.

- Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. *HRS reversal is defined as the percentage of subjects with*

a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques. The date RRT is instituted for the first time will be used to determine if a subject underwent RRT by Day 30. This endpoint will be *summarized by treatment group and* analyzed similarly to HRS reversal.

- Incidence of HRS reversal in the SIRS subgroup, defined as the percentage of SIRS subjects with HRS reversal. ~~SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded.~~ *HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).* This endpoint will be *summarized by treatment group and* analyzed similarly to HRS reversal. The SIRS subgroup is defined as any subject with at least 2 of the following criteria: WBC less than 4,000 or greater than 12,000 cells/μL; HR greater than 90 bpm; temperature greater than 38°C or less than 36°C; respiratory rate of greater than 20/min; HCO_3 less than 21 mmol/L; the latter criterion represents an approximation of the SIRS criterion $PaCO_2$ of less than 32 mm Hg, derived from the observed HCO_3 in subjects with HRS in whom a $PaCO_2$ value was available (from the TAHRS study) and the calculated HCO_3 in subjects with decompensated liver disease and $PaCO_2$ of less than 32 mm Hg.

- *Incidence of verified HRS reversal without* HRS recurrence by Day 30. HRS *Type 1* recurrence is ~~is another episode of HRS Type 1 as per the protocol inclusion/exclusion criteria~~ *defined in Section 10.5. Incidence of verified HRS reversal, defined as the percentage of subjects with two consecutive SCr values no more than 1.5 mg/dL at least 2 hours apart, while on treatment up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. This endpoint will be summarized by treatment group and analyzed similarly to HRS reversal.*

28. [redacted]

29. Section 15.3.8, Missing Data, was revised as follows:

    Unless otherwise stated, ~~N~~ no imputation will be made for missing data.

30. Section 20, References, was revised (additions in italics) to add the following citation:

    Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75:800-802.

31. Section 23, Appendix C: SAS Code and SAS Output was deleted (deletion not shown).

32. Other minor clarifications and grammatical corrections were made, which are not detailed.

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.

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]

[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:

Single-use, sterile 6-mL vials containing 1 mg of lyophilized terlipressin acetate (equivalent to 0.85 mg terlipressin free base) with 10 mg mannitol as a bulking agent/stabilizer. Each vial will be reconstituted with 5 mL of sterile 0.9% sodium chloride solution.

Reference Therapy, Dosage and Mode of Administration:

Matching placebo vials (containing 11 mg mannitol) that are identical in appearance to terlipressin for injection vials. Each vial will be reconstituted with 5 mL of sterile 0.9% sodium chloride solution.

The following dosing scheme will be utilized for both terlipressin and matching placebo:

Initial Dosing:

Blinded terlipressin or placebo will be administered intravenously as a bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (± 30 minutes).

Dose Modifications:

- If SCr has decreased, but by less than 30% from the baseline value on Day 4 after a minimum of 10 doses of study drug, the dose of study drug will be increased to 2 mg every 6 hours (± 30 minutes) (8 mg/day).
- The dose should not be increased in subjects with coronary artery disease or in the setting of circulatory overload, pulmonary edema, or bronchospasm.
- If dosing is interrupted due to an adverse event, study drug may be re-started, at the discretion of the investigator, at the same or lower dose as per protocol. Study drug will not be restarted if dosing was interrupted due to cardiac ischemia or mesenteric ischemia.
- If in the investigator's judgment, a dose increase is not advisable or otherwise justified in the individual subject, the reason(s) for not increasing the dose of study drug will be documented on the electronic case report form (eCRF).

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 (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14).

If on Day 4 (after a minimum of 10 doses) 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 (at least 30% reduction in SCr) who develop recurrence of HRS Type 1 during the study or follow-up period 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). Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine. **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 (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). • Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques. • Incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup, defined as the percentage of SIRS subjects with HRS reversal. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). • Incidence of verified HRS reversal without HRS recurrence by Day 30. HRS Type 1 recurrence is defined in Section 10.5. Incidence 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 up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.

[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). Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values collected after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from the primary endpoint analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine. 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, (150 subjects, with approximately 100 in the terlipressin group and 50 in the placebo group).
An O'Brien-Fleming spending function is used for the interim analysis alpha spending.

3 Table of Contents, List of Tables, and List of Figures

List of Tables

List of Figures

4 List of Abbreviations

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
ACLF	acute on chronic liver failure
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine amino transferase, also known as SGPT
ANCOVA	analysis of covariance
AR	adverse reaction
AST	aspartate amino transferase, also known as SGOT
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CG	Cockcroft-Gault
CrCl	creatinine clearance
CLIF-C	Chronic Liver Failure Consortium (organ failure score)
CLIF-SOFA	Chronic Liver Failure-Sepsis Organ Failure Assessment (score)
CMH	Cochran-Mantel-Haenszel
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EASL	European Association for the Study of the Liver
EVH	esophageal variceal hemorrhage
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRS	hepatorenal syndrome
IAC	International Ascites Club
IAC-AKI	IAC-acute kidney injury
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous

Abbreviation	Definition
IXRS	Interactive Voice and Web Response System
LVP	large volume paracentesis
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
MODS	multiorgan dysfunction syndrome
NDA	New Drug Application
NGAL	neutrophil gelatinase-associated lipocalin
NSAID	nonsteroidal anti-inflammatory drug
$PaCO_2$	partial pressure of arterial carbon dioxide
q4h	once every 4 hours
q6h	once every 6 hours
RBC	red blood cell
RRT	renal replacement therapy
SAE	serious adverse event
SUSAR	suspected unexpected adverse reaction
SCr	serum creatinine
SIRS	systemic inflammatory response syndrome
SpO_2	pulse oximetric saturation
TIPS	transjugular intrahepatic portosystemic shunt
US	United States
WBC	white blood cell
WHO	World Health Organization

5 Introduction

5.1 Hepatorenal Syndrome

Hepatorenal syndrome (HRS) Type 1, a potentially reversible renal failure, is a serious, rapidly progressing, fatal orphan disease complicating decompensated chronic liver disease associated with cirrhosis (Arroyo et al, 1996; Salerno et al, 2007; Angeli et al, 2015). The estimated United States (US) annual incidence for HRS Type 1 ranges between 9,000 and 20,000 patients (Marrero, 2003; Muir, 2002; Murkerjee et al, 2002; National Hospital Discharge Survey 2005), establishing it as an orphan disease. The death rate from chronic liver disease and cirrhosis has been rising, while the death rates for other major diseases such as stroke, cancer, heart disease, and diabetes have gone down in the past 15 years (Centers for Disease Control and Prevention 2013; Ma et al, 2015).

As indicated in the American Association for the Study of Liver Diseases (AASLD) Guidelines, at present, there is no available pharmacological therapy (ie, approved or proven) in the US or Canada for HRS Type 1 (Runyon, 2013) and there remains a significant unmet need.

An increasing body of knowledge of the pathophysiology of HRS Type 1 has demonstrated that vasoconstrictive drug therapy may improve renal function in HRS Type 1 (Salerno et al, 2007; European Association for the Study of the Liver 2010). Terlipressin has been extensively studied as a splanchnic vasoconstrictor for the treatment of HRS Type 1 and is the standard of care for this condition wherever the drug is available (European Association for the Study of the Liver 2010). Although there has been some off-label use of other vasoconstrictors, a recent study has shown that the most commonly used agents (ie, combination of midodrine and octreotide) are not effective (Cavallin et al, 2015).

5.2 Terlipressin

Terlipressin is a synthetic vasopressin analogue that acts as a systemic vasoconstrictor via the vascular vasopressin V_1 receptors. In HRS patients the strong V_1 receptor-mediated vasoconstrictor activity of terlipressin, particularly in the splanchnic area, increases effective intravascular volume and mean arterial pressure (MAP), ameliorates renin-angiotensin-aldosterone system and sympathetic nervous system hyperactivity, and improves renal blood flow. These corrective hemodynamic effects culminate in improved renal function, thereby providing the pharmacologic rationale for treatment of HRS with terlipressin (Arroyo et al, 2000; Ginès et al, 2003; Kiszka-Kanowitz et al, 2004).

After intravenous (IV) administration of terlipressin, the glycyl residues of terlipressin are cleaved by endogenous tissue proteases. Thus, terlipressin levels in the blood decrease rather rapidly and the pharmacologically active metabolite lysine-vasopressin is released gradually from tissues into the circulation.

Terlipressin is approved in many countries and regions outside the US where it has been the standard of care for decades in the treatment of subjects with liver cirrhosis and esophageal variceal hemorrhage (EVH) (de Franchis, 2005; Ioannou et al, 2003), and has more recently become a standard of care for the treatment of subjects with HRS Type 1 where it is available (EASL, 2010). Terlipressin has been approved for the treatment of HRS Type 1 in Australia, France, Ireland, South Korea, Mexico, Taiwan, Spain, India, Brazil, Turkey, and Portugal.

Refer to the Investigator's Brochure for a summary of the nonclinical studies with terlipressin.

5.3 Clinical Studies of Terlipressin in Subjects With HRS Type 1

Clinical data are available from 2 randomized, double-blind, placebo-controlled studies, (OT-0401 and REVERSE), a randomized, open-label, active-controlled study (TAHRS), and a large body of published literature studies in over 800 terlipressin-treated subjects with HRS Type 1 (Investigator's Brochure).

5.3.1 Pharmacokinetics and Pharmacodynamics

Following a 1-mg IV dose of terlipressin every 6 hours (q6h) in subjects with HRS Type 1 (OT-0401 and REVERSE studies), terlipressin has a median terminal half-life of approximately 0.9 hours. Although the half-life of lysine-vasopressin is short (1 to 6 minutes), as a result of the slow metabolic conversion of terlipressin to lysine-vasopressin the median apparent half-life of lysine-vasopressin is increased to approximately 3 hours.

Small transient changes in blood pressure and heart rate occurred 5 minutes after treatment with terlipressin and were likely attributable to the effect of terlipressin; maintaining these effects for 6 hours after treatment was most likely primarily attributable to the formation of lysine-vasopressin.

Refer to the Investigator's Brochure for further details.

5.3.2 Efficacy

Improvement in renal function is the goal of therapy for HRS Type 1; improvement in renal function is associated with improvement in clinical outcomes and improved prognosis, with or without liver transplantation. HRS reversal is a widely accepted, clinically meaningful response to treatment for HRS Type 1, as apparent inexorable, rapid progression of renal failure is arrested and normal renal function in the setting of decompensated liver disease is restored. The primary endpoint of HRS reversal (1 serum creatinine [SCr] value of no more than 1.5 mg/dL) is the standard endpoint utilized in the literature and HRS treatment guidelines (Arroyo et al, 1996; Salerno et al, 2007; Angeli et al, 2015).

The OT-0401 study (112 subjects with HRS Type 1 randomized 1:1 to receive terlipressin or placebo, with concomitant albumin administration recommended in both treatment arms) demonstrated a significantly higher rate of HRS reversal (34% vs 13%, p = 0.008) in the terlipressin treatment group compared to the placebo group. The primary endpoint of Treatment Success at Day 14 (an initial reduction of SCr to no more than 1.5 mg/dL followed by a confirmatory SCr measurement of no more than 1.5 mg/dL 48 hours after the initial HRS reversal and an additional SCr value less than 2.5 mg/dL at Day 14, without intervening liver transplant or dialysis) was also met following the incorporation of additional SCr values post initial database closure (29% vs 13%, p = 0.037). Furthermore, the prespecified endpoint of change in SCr from baseline to Day 14 demonstrated a greater reduction in SCr with terlipressin vs placebo (-0.9 mg/dL; p = 0.0008).

In the REVERSE study (196 subjects with HRS Type 1 randomized 1:1 to receive terlipressin or placebo, with concomitant albumin administration recommended in both treatment arms), there was a trend for greater HRS reversals with terlipressin treatment vs placebo (24% vs 15%, p = 0.129). For a number of reasons (for example, discharge from hospital before confirmatory laboratory values), statistical significance (20% vs 13%, not significant) was not achieved for confirmed HRS reversal (an initial reduction of SCr to no more than 1.5 mg/dL followed by a confirmatory SCr measurement of no more than 1.5 mg/dL 48 hours after the initial HRS reversal [in the case of hospital discharge or transplantation before 48 hours, the 2 confirmatory SCr values had to be at least 22 hours apart]). Although the REVERSE study did not meet the prespecified endpoint of HRS reversal, the prespecified endpoint of change in SCr from baseline to end of treatment demonstrated a greater reduction in SCr with terlipressin vs placebo (-0.6 mg/dL; p = 0.0002). This current study has been designed to address the methodological obstacles encountered in the REVERSE trial.

The open-label, active-controlled study (TAHRS) and a large body of published literature studies (including 44 published clinical investigations in over 800 terlipressin-treated subjects with HRS Type 1) have consistently demonstrated that terlipressin significantly improves renal function in subjects with HRS Type 1. In TAHRS, the incidence of HRS reversal was significantly higher in terlipressin + albumin-treated subjects compared with albumin-treated subjects (39.1% vs 8.7%; p = 0.018) and the change in SCr from baseline to the end of treatment was -0.7 mg/dL (p = 0.031). Data from the literature studies consistently showed clinically relevant improvements in renal function, as measured by reduction of SCr (eg, reversal of HRS or overall change in SCr), in 20% to 83% of subjects studied. Furthermore, the literature has been analyzed in a systematic fashion by external authors in 11 meta-analyses (7 of these meta-analyses included published data from the OT-0401 and TAHRS studies), which also confirm the efficacy of terlipressin for the treatment of HRS.

Refer to the Investigator's Brochure for further details.

5.3.3 Safety

Most subjects in both treatment groups in the OT-0401 and REVERSE studies experienced at least 1 adverse event (AE), which is expected given the high incidence of disease-related events in this severely ill patient population. The most commonly observed adverse reactions in terlipressin-treated subjects were abdominal pain and diarrhea (refer to Table of Adverse Drug Reactions in the Investigator's Brochure). Less common adverse reactions with clinical significance that were reported in terlipressin-treated subjects include: wheezing, respiratory failure, peripheral ischemia manifested as skin necrosis, peripheral coldness, livedo reticularis and Raynaud's phenomenon; intestinal ischemia including ischemic colitis; myocardial ischemia including myocardial infarction. The safety characteristics of terlipressin in the 2 studies were consistent with its vasoconstrictor mechanism of action. None of the events leading to discontinuation of terlipressin in either study were fatal and all resolved afterwards. Refer to the Investigator's Brochure for further details.

The safety characteristics of terlipressin observed in the 3 randomized, controlled trials is consistent with the established safety profile of terlipressin from 30 years of clinical experience, as captured in the literature and post-marketing data from the World Health Organization (WHO) database. There were no new, unusual or unexpected AEs observed in the clinical studies compared to the published data.

For detailed terlipressin safety risk profiling, please refer to the Investigator's Brochure.

In general, terlipressin has a well-established safety profile in the treatment of patients with HRS Type 1. The safety risks are predictable and recognizable. The adverse drug reactions can be readily managed and reversed by terlipressin dose reduction or interruption in hospital-care settings.

5.4 Study Rationale

The purpose of this randomized, placebo-controlled study is to confirm the efficacy and safety of terlipressin in the treatment of subjects with HRS Type 1 to provide data to support regulatory approval of the New Drug Application (NDA). Efficacy will be assessed through the primary endpoint of verified HRS reversal; other important efficacy parameters will be assessed including short-term durability of verified HRS reversal, magnitude of SCr lowering effect and effects in important subgroups (eg, systemic inflammatory response syndrome [SIRS] subgroup). Safety data will be collected and incorporated into the overall safety assessment of terlipressin. Methodological obstacles encountered in the REVERSE trial that reduced its ability to show statistical significance on the primary endpoint have been addressed in this trial design.

5.4.1 Primary Endpoint Rationale

HRS reversal, defined as at least 1 SCr measurement of no more than 1.5 mg/dL, has been used for decades to determine treatment response in published HRS clinical studies and is the standard endpoint utilized in the literature and in HRS treatment guidelines (Arroyo et al, 1996; Salerno et al, 2007; Angeli et al, 2015). The reversal of HRS Type 1 represents a dramatic clinical response to treatment: for the endpoint to be achieved, the rapid progression of renal failure must be arrested and normal renal function restored. The purpose of the primary end point of "verified" HRS reversal is to verify that the first SCr value of no more than 1.5 mg/dL is not a spurious laboratory value. An additional element of the primary endpoint requirement, ie, alive without RRT, has been added to demonstrate the short term durability of the primary end point on clinical outcomes. RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques.

5.4.2 Dosing Regimen and Recommended Concomitant Albumin Administration

The dosing regimen for the current study (see Section 10.3) will be the same as that used in OT-0401 and REVERSE. In OT-0401 and REVERSE, over 70% of subjects had no dose increase from the starting dose of 1 mg q6h and the majority of subjects who achieved HRS reversal responded at the 1 mg dose of terlipressin. Similarly, in the TAHRS study, the majority of subjects who achieved HRS reversal responded at the 1 mg every 4 hours (q4h) dose of terlipressin and all subjects who received a starting dose of 0.5 mg (q4h) (3 mg/day) had a dose increase to at least 1 mg q4h (6 mg/day). No clear dose response was evident from an examination of the literature, with doses of terlipressin in 44 published studies in HRS Type 1 ranging from 1 to 12 mg/day. Most studies allowed for dose increases after several days if no significant SCr decrease from baseline was observed.

As per standard medical practice, concomitant use of albumin in both treatment arms is strongly recommended, if clinically appropriate (Arroyo et al, 1996; Salerno et al, 2007; Angeli et al, 2015).

6 Objective

The objective of this study is to confirm the efficacy and safety of intravenous terlipressin vs placebo in the treatment of adult subjects with HRS Type 1 receiving standard of care albumin therapy.

6.1 Efficacy Variables

The efficacy variables are summarized below and further details are provided in Section 13.6.

6.1.1 Primary Efficacy Variables

The primary efficacy evaluation will be based on the following:

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). Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1,

was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.

Note: SCr data for primary end point will be collected at least daily until discharge or Day 14. The analysis will be based on the Intent to Treat (ITT) population.

6.1.2 Secondary Efficacy Variables

Secondary efficacy analyses will be based on the following:

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).

- Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques. The date RRT is instituted for the first time will be used to determine if a subject underwent RRT by Day 30.

- Incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup, defined as the percentage of SIRS subjects with HRS reversal. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).

Incidence of verified HRS reversal without HRS recurrence by Day 30. HRS Type 1 recurrence is defined in Section 10.5. 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 up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified

HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.

[redacted]

[redacted]

6.1.5 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.

7 Investigational Plan

7.1 Overall Study Design and Plan: Description

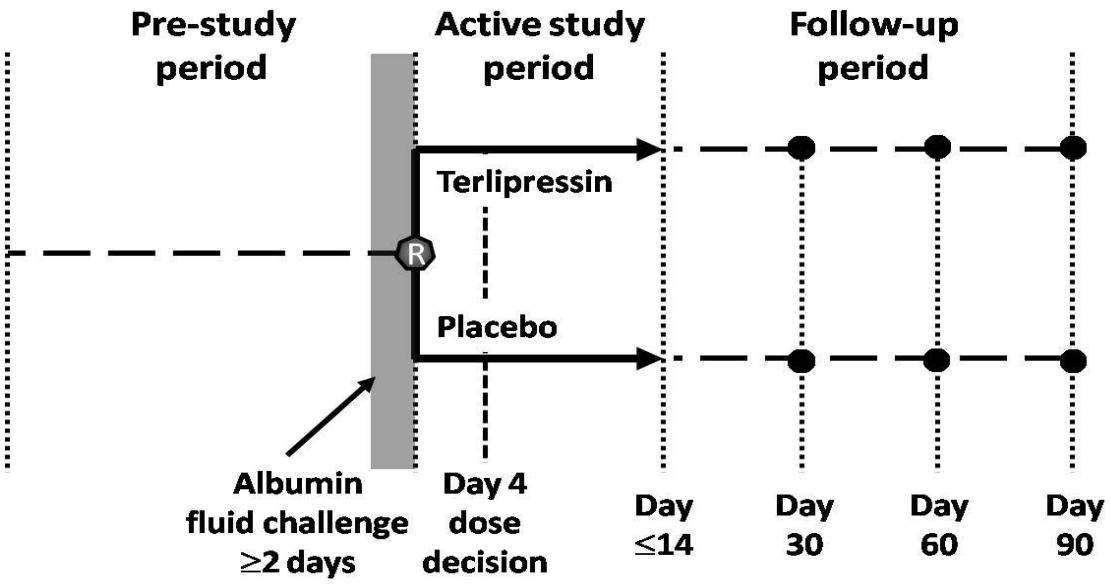
This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of intravenous terlipressin administered to subjects with HRS Type 1. All subjects who consent to study participation must undergo an in-hospital screening/qualification period of no less than 48 hours prior to enrollment in order to establish the diagnosis of HRS Type 1. Written informed consent will be obtained by the investigator, sub-investigator, or qualified designee from the subject or legally-authorized representative prior to the subject qualification form being completed. Qualified subjects will then be randomized in a 2:1 ratio to receive

either terlipressin or placebo, stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and pre-enrollment large volume paracentesis (LVP; at least one single event of at least 4 L or less than 4 L within 14 days prior to randomization). The qualifying SCr will be the last SCr that was on the screening/qualification eCRF. A total of 300 subjects are planned to be enrolled at approximately 70 sites in the US and Canada.

Subjects will receive up to 14 days of study treatment IV every 6 hours (± 30 minutes) (maximum of 15 days allowed if HRS reversal is first achieved on Day 14). Subjects will be contacted on Days 30 (±10), 60 (± 14), and 90 (± 14) for assessment of survival, RRT, TIPS, and liver transplant status (Figure 1).

Subjects will participate in 4 assessment periods, which includes screening, pre-treatment, active, and follow-up assessment (see Section 13.2).

Figure 1: Schematic Diagram of Study Design



8 Study Population

8.1 Population Rationale

The study population consists of adult subjects with cirrhosis, ascites, and a diagnosis of HRS Type 1 based on the IAC diagnostic criteria (Arroyo et al, 1996; Salerno et al, 2007; Angeli et al, 2015).

Subjects with a baseline SCr level greater than 7.0 mg/dL will be excluded from the study.

The threshold for upper cut-off of SCr in entry criteria is derived from the results of previous NDA studies. In OT-0401, none of the subjects with a baseline SCr level greater than 7.0 mg/dL achieved HRS reversal. Subjects will be stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL).

Qualifying SCr is a prognostic factor for survival and HRS reversal. Excluding subjects with a baseline SCr of greater than 7 mg/dL and LVP at least 4 L within 2 days prior to randomization (both are exclusion criteria for this study), 3.4 mg/dL (N = 253) was the median baseline SCr of subjects enrolled in the OT-0401 and REVERSE studies combined.

Subjects will also be stratified by pre-enrollment LVP (at least one single event of at least 4 L or less than 4 L within 3 to 14 days prior to randomization). Note, subjects with a LVP of at least 4 L are excluded if it occurs within 2 days prior to randomization (refer to Section 8.4).

As per the literature, a paracentesis was considered a LVP if at least 4 L of fluid was withdrawn in a given procedure (Choi et al, 2005; Kao et al, 1985; Ginès et al, 1987; Pinto et al, 1988; Tito et al, 1990). In REVERSE, there were significantly more placebo subjects who had at least 1 LVP (at least 4 L in a single procedure) within 14 days prior to enrollment (54 [54.5%] placebo subjects vs 36 [37.1%] terlipressin subjects, p = 0.0143) (prior LVP data were not collected in OT-0401). Subjects with a history of prior LVP exhibited an almost 3-fold greater verified HRS reversal rate with placebo compared to placebo-treated subjects without a history of prior LVP (18.5% vs 6.7%). The baseline imbalance increased the overall placebo response rate, contributing to the lower observed treatment effect.

The investigator must review any paracentesis performed in the pre-enrollment period and volume status after paracentesis must be considered carefully; as per standard of care, adequate replacement of fluid removed with albumin is required.

8.2 Number of Subjects to be Studied

A total of 300 subjects are planned to be enrolled at approximately 70 sites in the US and Canada. Discontinued subjects will not be replaced.

8.3 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to enrollment:

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 SCr at least 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks:
    - *Note:* Refer to Section 21 for a nomogram intended for use in situations when the SCr value has increased rapidly over a short period of time but has not yet doubled within 2 weeks. The nomogram may be used to determine whether the subject's SCr values are consistent with a trajectory likely to be representative of at least a doubling within 2 weeks (SCr values must be documented for a minimum of 4 days).
    - In situations where the time elapsed between SCr values is greater than 2 weeks, the investigator must contact the Medical Hotline maintained by the sponsor to discuss subject eligibility. The qualification form, including all available SCr data, must be completed by the investigator or qualified designee and forwarded to the sponsor for review and approval prior to enrollment. All communications between investigators and the sponsor regarding a subject's eligibility, including reasons supporting inclusion in the study, will be documented.
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:
    - *Note:* Albumin doses recommended by the IAC are 1 g/kg on the first day (maximum 100 g) and 20 g/day to 40 g/day thereafter as clinically indicated (Salerno et al, 2007; Angeli et al, 2015).

- *Note:* The qualifying SCr value is the SCr value at least 48 hours after both diuretic withdrawal (if applicable) and the beginning of albumin fluid challenge.
  The qualifying serum creatinine for subjects on prior vasopressors will be taken after completion of vasopressor washout. The qualifying SCr value must be at least 2.25 mg/dL AND at least 80% of the diagnostic (pre-fluid challenge) SCr value.
  No subjects should be randomized unless their SCr has been obtained within 8 hours prior to randomization and start of study drug. If there is a delay in subject randomization, then the qualifying/baseline SCr value must be redrawn so that the

value is collected within 8 hours prior to randomization and start of study drug to verify that the subject still meets the inclusion criterion for baseline SCr.

8.4 Exclusion Criteria

If any of the following exclusion criteria are met, the subject will **not** be enrolled:

1. Serum creatinine level greater than 7.0 mg/dL.
2. At least 1 event of LVP at least 4 L within 2 days of randomization.

   Note: The investigator must review any paracentesis performed in the pre-enrollment period and volume status after paracentesis must be considered carefully; as per standard of care, adequate replacement of fluid removed with albumin is required.
3. Sepsis and/or uncontrolled bacterial infection (eg, persisting bacteremia, persisting ascitic fluid leucocytosis, fever, increasing leucocytosis with vasomotor instability).

   Note: Sepsis is defined as documented active, untreated infection and presence of SIRS. SIRS is defined as the presence of 2 or more of the following findings: temperature greater than 38°C or less than 36°C; heart rate greater than 90/min; respiratory rate greater than 20/min or partial pressure of arterial carbon dioxide ($PaCO_2$) less than 32 mm Hg; white blood cell (WBC) count greater than 12,000 cells/μL or less than 4,000/ μL).

   Note: Patients with decompensated liver disease frequently have SIRS criteria in the absence of uncontrolled infection or sepsis. Subjects with SIRS criteria, in the absence of active, untreated infection, and reasonably attributed to decompensated liver disease or alternate causes (eg, hepatic hydrothorax, acute alcoholic hepatitis) should be enrolled after discussion with the sponsor via the Medical Hotline, assuming they meet all subject selection criteria.
4. Less than 2 days anti-infective therapy for documented or suspected infection.
5. Shock.

   Note: Shock is defined as hypotension (MAP less than 70 mm Hg or a decrease greater than 40 mm Hg in systolic blood pressure from baseline) with evidence of hypoperfusion abnormalities (eg, peripheral cyanosis, hypothermia, marked asthenia, pallor, obtundation not attributable to hepatic encephalopathy).

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.

   Note: Up to 3 doses of an NSAID within the prior month is acceptable.

   Note: Use of short-term (less than 2 weeks) oral neomycin for acute encephalopathy is acceptable.

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.

   Note: subjects meeting criteria for drug, dietary supplement or herbal preparation induced liver injury (http://livertox.nih.gov/; Chalasani et al, 2014) should be excluded
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) RRT.

15. Participation in other clinical research involving investigational medicinal products within 30 days of randomization.
16. 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 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.

NOTE: It is recognized that clinical judgment is a component of individual subject assessment, particularly in critically ill subjects with multi-organ disease. If, in the opinion of the investigator, a subject meets the criteria for HRS Type 1 but appears to demonstrate a potential deviation from the inclusion or exclusion criteria listed above, the investigator must contact the sponsor or designee via the Medical Hotline to discuss subject eligibility. All communications via the Medical Hotline, including reasons supporting inclusion in the study, will be documented.

8.5 Subject Withdrawal Criteria

Subjects have the right to discontinue treatment and/or withdraw from the study at any time without prejudice. The investigator may discontinue any subject at any time for any reason. If study treatment or protocol-specified assessments are discontinued, the reason will be recorded and the sponsor should be notified promptly. If a subject withdraws from the study, the reason will be recorded on the eCRF. Reasons for terminating participation in the clinical study may include the following:

- Adverse event(s).
- Abnormal laboratory value(s).
- Abnormal test procedure result(s).
- Protocol-noncompliance.
- Withdrawal of consent.

- Lost to follow-up.
- Administrative problems.

It is imperative to obtain complete follow-up data for all randomized subjects, whether or not they received their assigned study treatment, altered or discontinued study drug prematurely. Every attempt should be made to collect follow-up information, including required laboratory tests, serious adverse events (SAEs) and mortality assessments, except for those subjects who specifically withdraw consent for release of such information. Sites should contact subject/family member via telephone, mail or both to obtain this information. At least 3 documented attempts should be made by the site. Subjects withdrawn from treatment due to an adverse event should be followed until the event resolves, is no longer clinically significant, has stabilized, or is otherwise explained. Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up contact and from withdrawal of consent for non-subject contact follow-up (eg, medical records checks). Sites should do the utmost to obtain the withdrawal of consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing.

9 Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and wellbeing of the subject requires immediate intervention that deviates from the protocol, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or error, the investigator or designee must contact the sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. The investigator and the sponsor will document this decision. The Institutional Review Board (IRB) will be informed of all protocol deviations by the investigator in accordance with the IRB established procedure. No deviations from the protocol of any type will be made without complying with all the IRB established procedures.

10 Treatment of Subjects

10.1 Blinding

This study will be double-blinded using matching 6-mL placebo glass vials containing lyophilized mannitol without the active ingredient terlipressin, and 6-mL vials with lyophilized mannitol as the inert carrier compound containing 1 mg terlipressin acetate. Refer to Section 11.1 for details of the study drug and placebo.

10.2 Randomization

Subjects will be randomly assigned centrally using an interactive voice and web response system (IXRS) to treatment groups in order to minimize bias based upon subject selection and baseline characteristics. Subjects will be stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and pre-enrollment LVP (at least one single event of at least 4 L or less than 4 L within 3 to 14 days prior to randomization), and randomized (2:1) to receive either active terlipressin or matching placebo. Note, subjects with a LVP of at least 4 L are excluded if it occurs within 2 days prior to randomization (refer to Section 8.4).

Each investigational site will receive kits of blinded, labeled active and placebo vials each numbered with unique, randomized identification numbers. The method of unblinding will be through the IXRS. The randomization codes will be generated by an independent statistician and will not be accessible to blinded personnel (unless required during a medical emergency) during the study period.

10.3 Dosing With Study Drug

Each subject will be assigned blinded study drug. Under no circumstance is it permitted to treat a subject with study drug that was not specifically assigned to that subject.

10.3.1 Initial Dosing

Blinded terlipressin or placebo will be administered intravenously as a bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (± 30 minutes). After study drug administration, the line should be flushed with saline.

10.3.2 Dose Modifications

- If SCr has decreased, but by less than 30% from the baseline value on Day 4 after a minimum of 10 doses of study drug, the dose of study drug will be increased to 2 mg every 6 hours (± 30 minutes) (8 mg/day).

- The dose should not be increased in subjects with coronary artery disease or in the setting of circulatory overload, pulmonary edema, or bronchospasm.

- If dosing is interrupted due to an adverse event, study drug may be re-started, at the discretion of the investigator, at the same or lower dose as per protocol (refer to Section 10.3.2.1). Study drug will not be restarted if dosing was interrupted due to cardiac ischemia or mesenteric ischemia.

- If in the investigator's judgment, a dose increase is not advisable or otherwise justified in the individual subject, the reason(s) for not increasing the dose of study drug will be documented on the electronic case report form (eCRF).

10.3.2.1 Management of Adverse Events

With the exception of presumed cardiac or intestinal ischemia, the initial management of AEs may include dose reduction or temporary interruption of study drug dosing. After dose interruption, study drug may be restarted at a reduced dose of 0.5 mg or 1 mg every 6 to 12 hours. At the discretion of the investigator, the dose may then be increased to the previous dose level. Careful assessment of concomitant medications and treatment (particularly albumin dosing) and their potential relationship to the AE should be undertaken and adjusted as per standard of care and investigator discretion. If possible, study drug dosing should be restarted promptly and/or maintained at usual or reduced dosing particularly for the first 4 days of study drug administration. Investigators are encouraged to discuss any dosing questions with the Medical Hotline.

10.3.2.1.1 Management of Fluid Overload

Volume overload in this context refers to intravascular volume overload manifested as pulmonary congestion or overt pulmonary edema. Subjects with increasing dyspnea, cough, orthopnea, or tachypnea should be carefully evaluated for evidence of pulmonary edema (physical examination and, as judged by the investigator to be indicated, chest X-ray or other investigations). In subjects with fluid overload, especially those with respiratory events

(dyspnea, respiratory distress), careful assessment of concomitant albumin and temporary albumin dose reduction or discontinuance may be the most appropriate initial management. Judicious, short term use of temporary diuretic therapy as per standard of care may be undertaken at the discretion of the investigator in some subjects in whom a response to diuretic therapy is expected. If fluid overload requiring intervention persists after these initial measures, further management should include dose reduction or temporary interruption of study drug dosing as above.

10.4 Treatment Discontinuation

- Treatment should be continued until 24 hours after 2 consecutive SCr values no more than 1.5 mg/dL have been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14).

- If on Day 4 (after a minimum of 10 doses) 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.

10.5 Assessment of Recurrence

Any subject with a SCr value of at least 2.25 mg/dL after achieving verified HRS reversal, but prior to transplant/discharge/Day 14, will be assessed for HRS Type 1 recurrence. HRS recurrence by Day 30 is defined as another episode of HRS Type 1, by Day 30, after achieving verified HRS reversal, characterized by rapidly progressive worsening in renal function to a SCr at least 2.25 mg/dL, without 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, and meeting all applicable inclusion and exclusion criteria (as outlined in Section 8.3 and Section 8.4) defining the initial diagnosis of HRS Type 1.

Specifically, these criteria are as follows:

1. The subject had rapidly progressive worsening in renal function to a SCr at least 2.25 mg/dL and met a trajectory for SCr to double over 2 weeks.

2. The subject had 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.

3. The subject had no sepsis or uncontrolled bacterial infection.

4. If there is documented or suspected infection, the subject has at least 2 days of anti-infective therapy.

5. The subject does not have shock.

6. The subject does not have 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.

   Note: Up to 3 doses of an NSAID within the prior month is acceptable.

   Note: Use of short-term (less than 2 weeks) oral neomycin for acute encephalopathy is acceptable.

7. The subject had no superimposed acute liver injury or exposure to nephrotoxic agents.

8. Proteinuria was less than 500 mg/day.

9. The subject does not have evidence of obstructive uropathy or parenchymal renal disease on ultrasound or other imaging.

10. The subject does not have 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.

The investigator will determine whether the subject has had a recurrence of HRS Type 1. If the investigator cannot exclude a recurrence of HRS Type 1, then the subject will be considered to have HRS Type 1 recurrence. HRS Type 1 recurrence will be monitored as follows: Recurrence of HRS Type 1 during the follow-up period (after discharge or Day 14) will be assessed based upon the investigator's opinion and serious AE data collected up to 30 days after end of treatment. Following the initial hospital discharge, all re-hospitalizations within 30 days after end of treatment (except for planned hospital admissions or procedures as described in the protocol) are to be recorded as an SAE. Re-hospitalizations will require an investigator assessment and opinion regarding possible recurrence of HRS Type 1. All available relevant medical records, MedWatch forms, discharge summaries or other relevant source documents should be requested and reviewed for all SAEs, including all hospitalizations, until 30 days after discontinuation of study drug.

HRS Type 1 recurrence beyond 30 days after end of treatment will be further monitored based on requests for retreatment as outlined in Section 10.6 of the protocol.

10.6 Retreatment

If judged by the investigator to be potentially beneficial, subjects who demonstrate at least a partial response during the initial treatment course (at least 30% reduction in SCr) who develop recurrence of HRS Type 1 during the study or follow-up period 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 (Section 8.3 and Section 8.4) 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. Retreated subjects should follow the same schedule of assessment as performed in the original treatment period. The follow-up schedule will be based upon the original randomization. AEs for retreated subjects will be followed for 7 days postdose or discharge, whichever comes first.

10.7 Concomitant Medication

10.7.1 Recommended Concomitant Medication

10.7.1.1 Albumin

In keeping with standard medical practice and current guidelines, it is strongly recommended that albumin be administered to all subjects in both study arms. Albumin doses recommended by the IAC following the albumin fluid challenge are 20 g/day to 40 g/day as clinically indicated (Salerno et al, 2007; Angeli et al, 2015). It is recommended (if clinically appropriate) that the albumin dose is kept constant during the study drug administration period. For management of fluid overload, refer to Section 10.3.2.1.1.

10.7.1.2 Prohibited or Discouraged Concomitant Medications

The following medications are prohibited or strongly discouraged during treatment with study drug (Table 10–1).

Table 10–1 Prohibited/Discouraged Concomitant Medications

Prohibited Concomitant Medications
Midodrine and other vasopressive drugs including vasopressin, dopamine, dobutamine, norepinephrine.
Prostaglandin analogs (eg, misoprostol).
NSAIDs (eg, ibuprofen, naproxen, diclofenac).
Octreotide.
Discouraged Concomitant Medications
Diuretics are strongly discouraged unless medically required for fluid overload; limited use of diuretics for the management of fluid overload as per standard of care may be employed and must be documented (Section 10.3.2.1.1).

10.8 Treatment Compliance

The treatment, dosage and time of administration for each dose of study drug will be documented. A monitor will review subject source documents and drug accountability records to assess treatment compliance on an ongoing basis during site visits.

10.9 Medical Hotline

The sponsor will maintain a 24-hour medical hotline for investigators to discuss subject issues including enrollment eligibility, unblinding, and retreatment. The hotline number will be provided in the study manual. All hotline communications will be documented.

11 Study Drug Material and Management

11.1 Study Drug and Reference Therapy

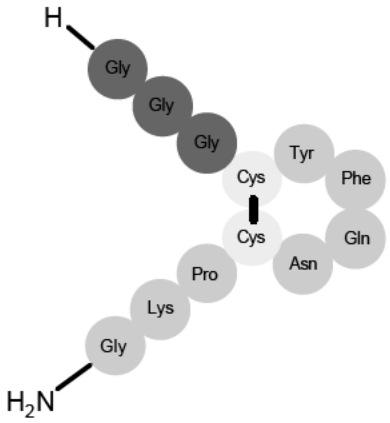
11.1.1 Terlipressin

The structure of terlipressin is presented in Figure 2. Single-use, sterile 6-mL vials containing 1 mg of lyophilized terlipressin acetate (equivalent to 0.85 mg terlipressin free base) with 10 mg mannitol as a bulking agent/stabilizer. Each vial will be reconstituted with 5 mL of sterile 0.9% sodium chloride solution.

The batch number will be documented in the trial master file.

Figure 2: Terlivaz® (Terlipressin for Injection)

Structure:



Molecular Formula: $C_{52}\ H_{74}\ N_{16}\ O_{15}\ S_2$

Molecular Weight: 1227.4 Daltons

Appearance: Homogenous lyophilized white to off-white solid

Solubility: Clear, colorless solution in saline

Vials:	Colorless glass vials containing 11 mg of a white to off-white solid, 1 mg active ingredient and 10 mg mannitol.

The active ingredient, N-[N-(N-glycylglycyl) glycyl]-8-L-lysinevasopressin, is a synthetically manufactured hormonogen of 8-lysine vasopressin, composed of 12 amino acids and having the characteristic ring structure of a cyclic nonapeptide with a disulfide bridge between the 4th and the 9th amino acid. Three glycyl-amino acids are substituted at position 1 (cysteine) of 8-lysine-vasopressin. By this N-terminal extension of 8-lysine-vasopressin, the metabolic degradation rate of the active ingredient is significantly reduced, because the glycyl molecules inhibit rapid N-terminal enzymatic degradation.

11.1.2 Placebo

Matching placebo vials (containing 11 mg mannitol) are identical in appearance to terlipressin for injection vials. Each vial will be reconstituted with 5 mL of sterile 0.9% sodium chloride solution.

11.2 Packaging and Labeling

Single-use, sterile 6-mL vials of a lyophilized solid containing 1 mg of terlipressin acetate (equivalent to 0.85 mg terlipressin free base) with mannitol or matching placebo (mannitol only) will be provided to the sites. Study drug labels will comply with local regulatory requirements, including sponsor name and address, protocol number, kit number, storage conditions and US Investigational New Drug (IND) caution statement.

11.3 Study Drug Storage and Preparation

Study drug should be stored in a secure location at 2ºC to 8ºC until reconstitution and can be stored up to 48 hours at refrigerated storage conditions (2ºC to 8ºC) once reconstituted with sterile 0.9% NaCl solution.

Access will be strictly limited to the investigators and their designees.

11.3.1 Reconstitution

Each vial of study drug will be reconstituted with 5 mL of sterile 0.9% sodium chloride solution.

11.3.2 Administration

Reconstituted study drug should be administered via a slow bolus (IV push over 2 minutes). See Section 10.1 for details.

After study drug administration the line should be flushed with saline.

11.4 Study Drug Accountability

The investigator or designee must maintain an inventory record of study drug administered to assure the regulatory authorities and the sponsor that the investigational new drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. Neither the investigators nor any designees may provide study drug to any subject not formally enrolled in this protocol.

The study drug supplied for use in this study is to be prescribed only by the investigator or named sub-investigators and may not be used for any purpose other than that outlined in this protocol.

All unused investigational product will be handled as outlined in the pharmacy manual. Periodic review of drug accountability records will be conducted by investigational site monitors. Final review and reconciliation of the accountability records will be performed by the sponsor or designee.

12 Randomization, Breaking of Blinded Codes

12.1 Randomization and Blinding

12.1.1 Randomization

After the subject has signed the informed consent form (ICF), the investigator or qualified designee will complete the subject qualification form, along with the required supportive documentation (including SCr values during hospitalization and details of albumin fluid challenge administration and diuretic withdrawal), and forward to the sponsor for review and approval of subject enrollment.

Randomization will occur only after a diagnosis of HRS Type 1 is established, written informed consent has been obtained from the subject or representative, and subject eligibility is confirmed. Once a subject is randomized, the subject is considered a study participant.

Even if study drug is not subsequently administered, the subject must be followed-up for mortality assessments.

A total of 300 subjects are planned to be randomized via an IXRS. Each successive subject will be assigned a unique identification number. Allocation will be made to 1 of 2 treatment groups, ie, terlipressin or placebo, in a 2:1 ratio. Both treatment groups will be studied concurrently. Randomization will be stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and pre-enrollment LVP (at least one single event of at least 4 L or less than 4 L within 3 to 14 days prior to randomization). Note, subjects with a LVP of at least 4 L are excluded if it occurs within 2 days prior to randomization (refer to Section 8.4).

12.1.2 Blinding of Study Drugs

The active and placebo vials will be labeled with single panel labels comprised of randomized identification numbers for each kit to maintain the blinding of the randomized treatments. Refer to the pharmacy manual for additional details.

12.1.3 Unblinding of Treatment Assignment

Unblinding of treatment assignment should be done only in the event that definite knowledge of the study drug is essential for the medical treatment of the subject. If possible, the investigator should contact the sponsor via the Medical Hotline prior to unblinding. In the event that unblinding of an individual subject is required, the investigator will be able to call into the IXRS system to unblind a subject.

The sponsor must be immediately informed of any unblinding and the site must document the date and reason for unblinding in writing, as well as the method used.

13 Assessments and Procedures

13.1 Schedule of Assessments and Procedures

Table 13–1 presents the schedule of assessments and procedures to be performed during the study.

Table 13–1 Schedule of Assessments

Study Assessment	Screening Period	Pre-Treatment Period	Active Study Period											Follow-up Period (Days from 1st Dose)[c]		
			Days 1 to 14[a] (as applicable)								End of Treatment	10 Days After 2nd SCR ≤ 1.5 mg/dL	Day 14[b] or Discharge whichever occurs first	30 days ± 10 d[t]	60 days ± 14 d	90 days ± 14 d
		Baseline Assessment	1	2	3	4	5	6	7	8 to 14[a]						
Diagnosis of HRS Type 1	X															
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Verification of study qualification	X															
Demographics	X															
Height and body weight	X															
Pregnancy test[d]	X															
Prior medications	X	X														
Record all pre-enrollment paracentesis prior to randomization[e,f]	X	X														
Baseline SCr prior to randomization[f]	X	X[g]														
Randomization		X														
Medical history[h]	X	X												X		

Study Assessment	Screening Period	Pre-Treatment Period	Active Study Period											Follow-up Period (Days from 1st Dose)[c]		
			Days 1 to 14[a] (as applicable)								End of Treatment	10 Days After 2nd SCR ≤ 1.5 mg/dL	Day 14[b] or Discharge whichever occurs first	30 days ± 10 d[t]	60 days ± 14 d	90 days ± 14 d
		Baseline Assessment	1	2	3	4	5	6	7	8 to 14[a]						
Physical examination (including weight and height)		X[i]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]				X[i]		
12-lead ECG[j]		X														
Child-Pugh score		X														
Urine sample for biomarkers[k]		X														
Blood sample for biomarkers[k]		X														
Venous blood lactate		X														
Study drug administration as applicable[l]			X	X	X	X	X	X	X	X						
Daily Assessments (regardless of treatment status)																
Record albumin dose administered		X	X	X	X	X	X	X	X	X	X		X			
SCr & BUN[m]		X	X	X	X	X	X	X	X	X	X		X	X[m]		

Study Assessment	Screening Period	Pre-Treatment Period	Active Study Period											Follow-up Period (Days from 1st Dose)[c]		
			Days 1 to 14[a] (as applicable)									10 Days After 2nd SCR ≤ 1.5 mg/dL	Day 14[b] or Discharge whichever occurs first			
		Baseline Assessment	1	2	3	4	5	6	7	8 to 14[a]	End of Treatment			30 days ± 10 d[t]	60 days ± 14 d	90 days ± 14 d
Confirmatory SCr at minimum of 2 hours after initial SCr of ≤ 1.5 mg/dL			X	X	X	X	X	X	X	X	X		X[n]			
Site to confirm subject survival for verified reversal[o]												X				
Record open label vasopressor use[p]			X	X	X	X	X	X	X	X	X		X			
Assessments ONLY On Treatment During Days 1 to 14																
Vital signs[q]		X	X	X	X	X	X	X	X	X	X			X		
Encephalopathy score		X	X	X	X	X	X	X	X	X						
Serum electrolytes		X	X	X	X	X	X	X	X	X	X					
ALT, AST, ALP, protein, albumin, bilirubin		X	X		X				X		X					
Serum glucose, calcium, magnesium		X	X		X				X		X					
INR		X	X		X				X		X					

Study Assessment	Screening Period	Pre-Treatment Period	Active Study Period											Follow-up Period (Days from 1st Dose)[c]		
			Days 1 to 14[a] (as applicable)								End of Treatment	10 Days After 2nd SCR ≤ 1.5 mg/dL	Day 14[b] or Discharge whichever occurs first	30 days ± 10 d[t]	60 days ± 14 d	90 days ± 14 d
		Baseline Assessment	1	2	3	4	5	6	7	8 to 14[a]						
CBC and differential		X	X		X				X		X					
Concomitant medications[r]			X	X	X	X	X	X	X	X				X		
Assessments Throughout Study																
Adverse events			Monitor and record throughout active study period to 7 days post-treatment for AEs, 30 days post-treatment for SAEs.											X		
HRS Type 1 recurrence assessment			Monitor and record throughout active study period and follow-up.													
Record events of RRT, TIPS, transplant, and mortality[s]			Monitor and record throughout active study period and follow-up.													

Study Assessment	Screening Period	Pre-Treatment Period	Active Study Period										Follow-up Period (Days from 1st Dose)[c]		
			Days 1 to 14[a] (as applicable)								End of Treatment	10 Days After 2nd SCR ≤ 1.5 mg/dL	Day 14[b] or Discharge whichever occurs first	30 days ± 10 d[t]	60 days ± 14 d	90 days ± 14 d
		Baseline Assessment	1	2	3	4	5	6	7	8 to 14[a]						
Record all paracentesis events			Record all paracentesis performed after study drug treatment discontinued to 30-day follow-up													

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CBC = complete blood count, d = day; ECG = electrocardiogram, HRS = hepatorenal syndrome, INR = international normalized ratio, LVP = large volume paracentesis, RRT = renal replacement therapy, SCr = serum creatinine, TIPS = transjugular intrahepatic portosystemic shunt.

[a]Same procedures and assessments on Day 15 if response first occurs on Day 14.

[b]Day 15 if response first occurs on Day 14.

[c]Follow-up assessments must also be completed for subjects randomized but not treated with study drug. Study days will be counted from first day of study drug administration (or from randomization for those subjects who do not receive study drug).

[d]Female subjects of child-bearing potential must have a negative urine or serum pregnancy test within 14 days prior to the first dose of study treatment.

[e]Date and volume of all pre-enrollment paracentesis will be recorded in the eCRF.
Note, subjects with a LVP of at least 4 L are excluded if it occurs within 2 days prior to randomization (refer to Section 8.4).
The investigator must review any paracentesis in the pre-enrollment period and volume status after paracentesis must be considered carefully; as per standard of care, adequate replacement of fluid removed with albumin is required. A paracentesis is considered a LVP if at least 4 L of fluid is withdrawn in a given procedure (Choi et al, 2005; Kao et al, 1985; Ginès et al, 1987; Pinto et al, 1988; Tito et al, 1990).

[f]All pre-enrollment paracentesis and baseline SCr to be recorded before randomization (and required for IXRS).

[g]The qualifying SCr value (SCr value at least 48 hours after both diuretic withdrawal and the beginning of albumin fluid challenge) is considered the baseline SCr and must be drawn no more than 8 hours prior to start of study drug. The qualifying SCr value must be at least 2.25 mg/dL AND at least 80% of the diagnostic (pre-fluid challenge) SCr value.
No subjects should be randomized unless their SCr has been obtained within 8 hours prior to randomization and start of study drug.
If there is a delay in subject randomization, then the qualifying/baseline SCr value must be redrawn so that the value is collected within 8 hours prior to randomization and start of study drug to verify that the subject still meets the inclusion criterion for baseline SCr.

[h]Medical history will include assessment of multi-organ dysfunction at baseline (refer to Section 13.3.5 and the Site/Investigator Study Manual for additional details).

[i]A general physical assessment of the major body systems evaluating any new clinically significant abnormalities within the following: general appearance, skin, head/eyes/ears/nose/throat, neck, heart, lungs, abdomen, extremities, and neurological systems, the physical examination will also include weight and height.

[j]A 12-lead ECG will be performed at baseline. Clinically relevant abnormalities found will be reported on the medical history page. The investigator may perform additional unscheduled examinations to manage or evaluate a suspected AE as clinically necessary.

[k]Both urine and blood samples for biomarker evaluation will be collected once at baseline; participation in this project will not affect participation in the main study.

[l]Treatment should be continued until 24 hours after 2 consecutive SCr values no more than 1.5 mg/dL have been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14, when the Day 14 assessments will be performed on Day 15). Window is (± 30 minutes).

[m]Must be performed at least once daily during active treatment AND until Day 14 (regardless of treatment status) or discharge, whichever occurs first. If SCr and/or BUN assessments are performed more than once daily as part of the subject's medical care, all values are to be recorded on the eCRF. At 30-day follow-up visit, collect SCr only (no BUN).

[n]A blood sample for measurement of SCr must be drawn before discharge. The second verifying sample of SCr no more than 1.5 mg/dL must be taken at least 2 hours apart and must be consecutive.

[o]If a subject meets the primary end point (2 consecutive SCr values of no more than 1.5 mg/dL), the subject's survival and RRT status must be confirmed 10 days after the date of the second SCr. This follow up is required regardless of whether the subject remains hospitalized or has been discharged. If the subject has been discharged, follow-up may be by phone.

[p]Required for evaluation of efficacy endpoints.

[q]Vital sign measurements include body temperature, respiratory rate, systolic and diastolic blood pressure, SpO_2 (pulse oximetric saturation), and heart rate. Time points for systolic and diastolic blood pressure and heart rate: predose and postdose at 5 (±2) min and 2 (±0.25) h for every dose. Time points for body temperature, respiratory rate, and pulse oximetric saturation (SpO_2): once daily.

[r]Concomitant medications include IV solutions and blood products.

[s]All subjects will be required to come back for Day 30 (± 10) visit and will be contacted by phone for Day 60 (± 14), and Day 90 (± 14) follow up to assess survival, RRT, TIPS and liver transplant status. Study days will be counted from first day of study drug administration (or from randomization for those subjects who do not receive study drug). All information regarding RRT, TIPS and liver transplant must be collected.

[t]For the Day 30 follow-up visit, all subjects are required to provide a blood sample for SCr. The site staff must also collect an updated medical history, vital signs, concomitant medications, SAE assessment, paracentesis events, RRT, and HRS recurrence.

[u]The investigator should perform daily abbreviated physical examinations through the end of treatment to evaluate suspected AEs.

13.2 Study Assessment Periods

13.2.1 Screening Period

The screening period occurs prior to enrollment and consists of establishing the diagnosis of HRS Type 1 as per guidelines and standard medical practice and confirming eligibility for study participation. The investigator or qualified designee will complete the subject qualification form along with the required supportive documentation (including SCr values during hospitalization and details of albumin fluid challenge administration and diuretic withdrawal) and forward to the sponsor for review and approval of subject enrollment. Written informed consent will be obtained by the investigator, sub-investigator, or qualified designee from the subject or legally authorized representative prior to the subject qualification form being completed.

Subjects screened but not enrolled in the study for any reason should be recorded on the screening log. These subjects are not considered study participants and no additional follow-up is required.

The investigator must review any paracentesis performed in the pre-enrollment period and volume status after paracentesis must be considered carefully; as per standard of care, adequate replacement of fluid removed with albumin is required.

13.2.2 Pre-Treatment Period

The pre-treatment period occurs prior to administration of study drug and includes performing baseline assessments and collection of prior medication information.

- The qualifying SCr value (SCr value at least 48 hours after both diuretic withdrawal and the beginning of albumin fluid challenge) is considered the baseline SCr and must be drawn no more than 8 hours prior to start of study drug. The qualifying SCr value must be at least 2.25 mg/dL AND at least 80% of the diagnostic (pre-fluid challenge) SCr value. No subjects should be randomized unless their SCr has been obtained within 8 hours prior to randomization and start of study drug. If there is a delay in subject randomization, then the qualifying/baseline SCr value must be redrawn so that the value is collected within 8 hours prior to randomization and start of study drug to verify that the subject still meets the inclusion criterion for baseline SCr. The qualifying serum creatinine for subjects on prior vasopressors will be taken after completion of vasopressor washout. Other baseline assessments must be performed no more than 24 hours prior to start of study drug.

13.2.3 Active Study Period (14 Days)

13.2.3.1 Dosing (Up to 14 Days)

The active study period extends from the initiation of study treatment through Day 14 (Day 15 as described in Section 10.4) or discharge from the hospital for any reason, whichever occurs first. Study drug will be administered as described in Section 10.3. Concomitant medications will be collected during this active study period.

See Table 13–1 for the schedule of assessments during the active study period.

13.2.3.2 End of Treatment, Discharge or Day 14

Treatment should be continued until 24 hours after 2 consecutive SCr values no more than 1.5 mg/dL have been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14, when the Day 14 assessments will be performed on Day 15).

Following HRS reversal (SCr no more than 1.5 mg/dL), repeat values for SCr must be obtained a minimum of 2 hours after the first SCr value. Every effort must be made to collect these SCr values.

All information regarding paracentesis events, RRT, TIPS, liver transplant, or open-label vasopressor use must be collected.

The subject will be contacted to determine the status of survival without RRT at 10 days after the second SCr value no more than 1.5mg/dL is attained.

13.2.4 Follow-up Period

The follow-up period begins after the end of the study treatment and concludes 90 days following the start of treatment. Study days will be counted from first day of study drug administration (or from randomization for those subjects who do not receive study drug).

All subjects will have a follow up visit on Day 30 (±10 days) while Day 60 (± 14), and Day 90 (± 14) follow up can be done via telephone to assess survival, RRT, TIPS, and liver transplant status. Study days will be counted from first day of study drug administration (or from randomization for those subjects who do not receive study drug). In addition, during the Day 30 follow-up, a blood sample will be obtained to assess serum creatinine. A physical examination, updated medical history, vital signs, concomitant medications, and SAE assessments, paracentesis events, RRT, TIPS, and liver transplant status will also be collected.

13.2.4.1 Day 30 Blood Sample Collection

All subjects will be required to provide a blood sample at Day 30 (± 10 days) for analysis of SCr. This blood sample can be drawn during the Day 30 visit or by a visiting phlebotomist if the subject is unable to return to the study site during the Day 30 follow-up window. Every effort will be made to collect a blood sample at Day 30 for all subjects. No imputation will be made for missing values.

13.3 Detail of Baseline Assessments and Procedures

13.3.1 Physical Examination

A complete physical examination, including weight and height, will be conducted at baseline and at the 30-day follow-up. This will include a general physical assessment of the major body systems evaluating any new clinically significant abnormalities within the following: general appearance, skin, head/eyes/ears/nose/throat, neck, heart, lungs, abdomen, extremities, neurological, back/spinal, and lymph nodes. This includes worsening of baseline conditions.

In addition, abbreviated physical examinations will be conducted every day during the 14-day active study period.

The investigator may perform additional unscheduled examinations to manage or evaluate a suspected AE as clinically necessary. The timing and scope of additional unscheduled examinations should be determined by the nature and severity of the AE being evaluated. In the case of suspected cardiac, intestinal or other ischemia, examination of the subject by a physician should be completed on an emergency basis (generally within 15 to 30 minutes). For suspected cardiac ischemia, examination should include assessment of vital signs, cardiac and pulmonary auscultation, and evaluation of jugular venous pressure by clinical examination and other components as determined by the physician's clinical judgment. For suspected cardiac ischemia, site must perform an ECG and cardiac enzymes (high sensitivity troponin) at the time of assessment and 3 hours later. Subjects with suspected intestinal ischemia should undergo careful examination of the abdomen to evaluate for the presence of diffuse or focal tenderness, rebound, or acute abdomen with diffuse rigidity. For suspected intestinal ischemia, venous (blood) lactate levels must be drawn and compared to baseline levels. Further investigations should be carried out based on clinical practice. All subjects should have evaluation of the skin of the trunk and extremities for mottling, cyanosis, blanching or pallor.

Clinically relevant abnormalities found upon physical examination will be reported and analyzed as AEs.

13.3.2 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at baseline. Clinically relevant abnormalities found will be reported on the medical history page. The investigator may perform additional unscheduled examinations to manage or evaluate a suspected AE as clinically necessary. Clinically relevant abnormalities found upon subsequent ECGs will be reported and analyzed as AEs. The dates of all subsequent ECGs will be reported on the ECG eCRF.

13.3.3 Child-Pugh Scores

Child-Pugh score will be calculated at baseline and entered in the eCRF.

13.3.4 Vital Signs

The proposed post-study-drug time points for collection of systolic/diastolic blood pressure and heart rate are based on PK data from the OT-0401 and REVERSE clinical trials. The 5 (±2) min and 2 (±0.25) h time points roughly coincide with peak plasma concentrations of terlipressin and lysine-vasopressin respectively. Refer to Section 13.4.1.

13.3.5 Assessment of Multi-Organ Dysfunction

With the advancement in intensive care medicine, multiorgan dysfunction syndrome (MODS) has replaced the term multiorgan failure since the completion of the REVERSE study. According to Al-Khafaji et al, 2015, MODS describes a continuum with incremental degrees of physiologic derangements in individual organs; a process rather than a single event. Alteration in organ function can vary widely from a mild degree of organ dysfunction to completely irreversible organ failure.

Multi-organ failure or dysfunction, a hallmark of acute on chronic liver failure (ACLF), common in the study patient population, is defined and quantified by the original CLIF-SOFA score or its simplified version Chronic Liver Failure Consortium (CLIF-C) Organ Failure score (Arroyo et al, 2015). The scoring system has been developed and validated for predicting mortality in patients with ACLF (Jalan et al, 2014).

Table 13–2 CLIF-C Organ Failure Score

Organ System	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dL)	< 6	6 to ≤ 12	> 12
Kidney, creatinine (mg/dL)	< 2	2 to < 3.5	≥ 3.5 or renal replacement
Brain, grade (West-Haven)	0	1 to 2	3 to 4
Coagulation, INR	< 2.0	2.0 to < 2 .5	≥ 2.5
Circulation, MAP (mm Hg)	≥ 70	< 70	Vasopressors
Respiratory PaO_2/FiO_2	> 300	≤ 300 and > 200	≤ 200
or SpO_2/FiO_2	> 357	> 214 and ≤ 357	≤ 214

Source: Arroyo et al, 2015.
Abbreviations: FiO_2 = fraction of inspired oxygen; INR = international normalized ratio; MAP = mean arterial pressure; PaO_2 = partial pressure of arterial oxygen; SpO_2 = pulse oximetric oxygen saturation.

During baseline information collection and adverse event reporting, the investigators are required to record the actual organs involved in MODS (ie, other organs involved in MODS in addition to the baseline hepatic and renal dysfunction, and the severity of dysfunction in each organ involved), as well as MODS, itself, as a disease state. The use of the simplified version CLIF-C Organ Failure scoring system in documenting MODS organ involvement and MODS severity is strongly encouraged. Assessment of MODS will be detailed in the Site/Investigator Study Manual.

13.4 Detail of Safety Assessments and Procedures

13.4.1 Vital Signs

Vital sign measurements will be recorded at baseline (with the physical examination), during study drug administration, at the end of treatment, and at the Day 30 follow-up.

Systolic and diastolic blood pressure and heart rate will be recorded at baseline, and pre-dose and post-dose at 5 minutes (± 2 min) and 2 hours (± 0.25h) for every dose.

Body temperature, respiratory rate, and pulse oximetric saturation (SpO_2) will be recorded once daily at baseline and during study drug administration.

13.4.2 Encephalopathy Score

Clinically detectable encephalopathy is to be assessed prior to study drug administration and daily during study drug administration using the clinical criteria described in Table 13–3.

Table 13–3 West Haven Criteria for Semiquantitative Grading of Mental State

Grade 1	Trivial lack of awareness. Euphoria or anxiety. Shortened attention span. Impaired performance of addition.
Grade 2	Lethargy or apathy. Minimal disorientation for time or place. Subtle personality change. Inappropriate behavior. Impaired performance of subtraction.
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli. Confusion. Gross disorientation.
Grade 4	Coma (unresponsive to verbal or noxious stimuli).

Source: Ferenci et al, 2002.

13.4.3 Model for End-Stage Liver Disease Score

Model for end-stage liver disease (MELD) scores will be calculated by the sponsor based on SCr, bilirubin and INR values at baseline and treatment Days 1, 3, 7 and treatment termination.

13.4.4 Adverse Events

All adverse events will be assessed and recorded beginning with study drug administration until 7 days after discontinuation of study drug. Adverse events considered serious will be assessed and recorded until 30 days after discontinuation of study drug; excluding deaths, which will be collected up to 90 days after the first dose of study drug.

Those events that are serious in nature must be reported to the sponsor or its designee for safety reporting in an expedited manner (see Section 14 for definitions and reporting requirements).

The adverse event collection schedule for the proposed study is adopted from the previous clinical studies in the same patient population and for the same drug. The time frames for collecting various types of adverse events are defined to focus on the collection of safety information pertinent to the study subjects in the proposed study, as the target patient population has an extensive health background and existing medical conditions.

13.4.4.1 Adverse Events of Special Interest

Based on its known mechanism of action and pharmacodynamics effects, terlipressin treated subjects may develop central or peripheral ischemia and signs/symptoms of pulmonary congestion including bronchospasm, wheezing, etc. To better characterize and help conduct a thorough safety analysis for these events, additional information will be requested from study sites for subjects who report AEs of select MedDRA preferred terms. These AEs will be considered as adverse events of special interest and will include abdominal pain, chest pain or dyspnea/wheezing/bronchospasm/pulmonary edema. Sites will be required to complete an additional Adverse Events of Special Interest eCRF page and provide information, ie, characteristics of the event (location, time course, aggravating/relieving factors) as well as clinical laboratory and other investigations including radiologic imaging studies conducted in relation to the reported event.

13.5 Detail of Laboratory Assessments and Procedures

13.5.1 Local Laboratory at Investigational Site

The laboratory tests specified in this section will be performed in the laboratory at the investigational site. All local laboratories must use the isotope dilution mass spectroscopy method for the serum creatinine assay. All efforts should be made to take the blood sample from a clean new venous site, or the second option could be a central venous line to collect the blood specimen. Site personnel should not draw the blood sample from an existing peripheral venous access site or a line used for IV fluid administration. See Site/Investigator's Study Manual for additional details regarding blood drawing technique.

13.5.1.1 Serum Electrolytes & Biochemistry

The following assessments are required at baseline, then once daily during treatment (max 15 days), daily until Day 14 or hospital discharge (whichever occurs first), and at the 30-day follow-up visit, regardless of treatment status:

- Creatinine level.
- Blood urea nitrogen (BUN) (not collected at 30-day follow-up).

If SCr and/or BUN assessments are performed more than once daily as part of the subject's medical care, all values are to be recorded on the eCRF.

The following assessments are required at baseline, then once daily during treatment with study drug (max 15 days):

- Sodium.
- Potassium.
- Chloride.
- HCO_3.

The following assessments are required at baseline, on Treatment Days 1, 3, 7, and whenever possible, at treatment termination:

- Total bilirubin.
- Alkaline phosphatase (ALP).
- Alanine aminotransferase (ALT).
- Aspartate aminotransferase (AST).
- Total protein.
- Albumin.
- Magnesium.
- Calcium.
- Glucose.

13.5.1.2 Hematology

The following assessments are required at baseline, on Treatment Days 1, 3, 7, and whenever possible, at treatment termination:

- International normalized ratio (INR).
- Complete blood count (CBC) and differential.

13.5.2 Total Volume of Blood Collected

The total volume of blood collected from each subject over the course of 14 days and end of study will be approximately 310 mL.

If subjects agree to participate in the biomarker study an additional blood sample of approximately 10 mL will be collected.

13.6 Detail of Efficacy Assessments and Procedures

Serum creatinine must be collected at baseline, once daily during treatment (see Section 13.5.1.1); and then once daily (regardless of treatment status) until Day 14 or hospital discharge, whichever occurs first. If SCr assessments are performed more than once daily as part of the subject's medical care, all values obtained each day will be recorded on the eCRF. Serum creatinine values obtained after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from the efficacy evaluation. The qualifying serum creatinine for subjects on prior vasopressors will be taken after completion of vasopressor washout.

13.6.1 Primary Efficacy Variable

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). Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from primary endpoint analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.

SCr data for the primary end point will be collected at least daily until discharge or Day 14. The analysis will be based on ITT population. Treatment should be continued until 24 hours after a second confirmatory SCr value no more than 1.5 mg/dL has been obtained, OR up to a maximum of 14 days (maximum of 15 days if SCr first reaches 1.5 mg/dL on Day 14). The date and time of the first observed SCr value of no more than 1.5 mg/dL (HRS reversal) will be used for calculating the time window for the verifying SCr value. The next (consecutive) SCr value of no more than 1.5 mg/dL must occur during the time window in order to have a verified HRS reversal. The date RRT is instituted for the first time will be used to determine if a subject underwent RRT by Day 30.

13.6.2 Secondary Efficacy Variables

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded).

- Durability of HRS reversal: the percentage of subjects with HRS reversal without RRT to Day 30. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques. The date RRT is instituted for the first time will be used to determine if a subject underwent RRT by Day 30.

- Incidence of HRS reversal in the SIRS subgroup: the percentage of SIRS subjects with HRS reversal. HRS reversal is defined as the percentage of subjects with a SCr value no more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). The SIRS subgroup is defined as any subject with at least 2 of the following criteria: WBC less than 4,000 or greater than 12,000 cells/µL; heart rate greater than 90 bpm; temperature greater than 38°C or less than 36°C; respiratory rate greater than 20/min; HCO_3 less than 21 mmol/L; the latter criterion represents an approximation of the SIRS criterion $PaCO_2$ of less than 32 mm Hg, derived from the observed HCO_3 in subjects with HRS in whom a $PaCO_2$ value was available (from the TAHRS study) and the calculated HCO_3 in subjects with decompensated liver disease and $PaCO_2$ of less than 32 mm Hg.

Incidence of verified HRS reversal without HRS recurrence by Day 30 is defined in Section 10.5. 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 up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August

2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.

[redacted]

[redacted]

14 Adverse Events

The investigator will carefully collect a thorough first dose of study drug baseline information and history for each subject upon enrollment. Immediately after a subject receives the first dose of study drug, throughout the duration of the study treatment and at each evaluation, the investigator will determine whether any AE has occurred. The investigator will also instruct the subject to contact the investigator or designee in between study visits and throughout the entire study period to report any AEs, until otherwise instructed.

The investigator will record the nature, causality, severity, treatment and outcome of the AE, and will determine whether there is a "reasonable probability" that the study drug treatment caused the event.

A data safety monitoring board (DSMB) will review safety data throughout the study, as outlined in the DSMB charter.

14.1 Definitions

The following definitions are based on:

- International Council for Harmonisation (ICH) E2A: International Conference on Harmonisation Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994).
- ICH E6: International Council for Harmonisation Tripartite Guideline: Guideline for Good Clinical Practice (1996) and Integrated Addendum [E6] (R2) June 2015.
- Office of Human Subjects Protection, Division of Department of Health and Human Services Policy; "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" (2007).
- Code of Federal Regulations Title 21, Part 312.32 (2011).

Also included are events that are common to this subject population.

14.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

14.1.2 Adverse Reaction Definition

An adverse reaction (AR) is defined as any AE caused by a drug.

In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug

reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

14.1.3 Suspected Adverse Reaction Definition

A suspected adverse reaction is defined as an AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility suggests a causal relationship between the study drug treatment and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an AE.

14.1.3.1 Unexpected Adverse Drug Reaction Definition

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

14.1.4 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction Definition

This is an AE or suspected unexpected adverse reaction (SUSAR) which is not listed in the Investigator’s Brochure (IB), nor listed at the specificity or severity observed. If an AE or SUSAR is listed in the IB as occurring with a specific class of drugs, or occurring as part of a disease process, or from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation, it should be considered unexpected.

14.1.5 Treatment Emergent Adverse Event Definition

An AE for which the start date is on or after the date that the intervention begins.

14.1.6 Serious Adverse Event Definition

Serious adverse events (SAE) are a subset of adverse events. They are defined (in the view of the investigator or the sponsor) as any untoward medical occurrence that meets any of the following criteria:

- Resulted in death.
- Is life-threatening (if an AE or SUSAR places a subject at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in disability (persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of an important medical event include: allergic bronchospasm, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or drug dependence/abuse.

14.1.7 Severity of an Adverse Event

Intensity of an AE, assessed by the investigator and graded as mild, moderate or severe, irrespective of the relationship to the drug or seriousness of the event, and evaluated according to the following scales:

- Mild - awareness of the symptom but easily tolerated.
- Moderate - discomfort enough to interfere with normal activities.
- Severe - Incapacitating with the inability to perform normal activities.

An AE not listed in the IB at the specificity or severity observed is considered unexpected.

14.1.8 Study Drug Causality

Study drug causality will be assessed as follows:

Unrelated: An AE that is clearly and incontrovertibly due to extraneous causes (disease, environment, etc) and does not meet the criteria for 'possible' or 'probable.'

Possible: The connection between the AE and study treatment appears unlikely, but cannot be ruled out with certainty. An AE may be considered 'possibly related' if it has at least 2 of the following:

- It follows a reasonable temporal sequence from administration of study drug.
- It may readily have been produced by the subject's clinical state or by environmental or toxic factors.
- It follows a known response pattern to study drug.

Probable: An AE that is considered to be related to study drug treatment with a high degree of certainty. An AE may be considered probably related if:

- It follows a reasonable temporal sequence from administration of study drug.
- It cannot be reasonably explained by the known characteristics of the subject's clinical state.
- It follows a known pattern of response to study drug treatment.
- It reappears upon rechallenge.

Table 14–1 lists adverse events that are common in this subject population (ie, with HRS), even in the absence of exposure to the study drug (Rozov-Ung and Panesar, 2010; Arroyo et al, 2008).The investigator may use this as a guidance while assessing the causality. Adverse events will be analyzed in both an aggregate and individual manner. However, if it is deemed an AR, the sponsor will follow the appropriate procedures to communicate and report the AR.

Table 14–1: Adverse Events Common to the Hepatorenal Syndrome (HRS) Population

MedDRA System Organ Class	Preferred Term
Blood and Lymphatic System Disorders	anemia
	coagulopathy
Cardiac Disorders	atrial fibrillation
	bradycardia
Gastrointestinal Disorders	abdominal pain
	diarrhea
	nausea
	vomiting
General Disorders and Administration Site Conditions	multi-organ failure
Hepatobiliary Disorders	hepatic failure
Infections and Infestations	pneumonia
	urinary tract infection
Metabolism and Nutrition Disorders	hyperglycemia
Nervous System Disorders	headache
Respiratory, Thoracic and Mediastinal Disorders	dyspnea
	epistaxis
	pulmonary edema
	respiratory failure
Vascular Disorders	hypotension

Source: Rozov-Ung and Panesar, 2010; Arroyo et al, 2008.

14.1.9 Overdose

Overdose is defined as an accidental or intentional/infusion or excessive dose of a product.

14.2 Collection of Adverse Events/Serious or Unexpected

Any AE occurring prior to signing the ICF should be considered medical history or a pre-existing condition and will be collected on the Medical History eCRF.

All AEs will be assessed and recorded beginning with study drug administration until 7 days after discontinuation of study drug and at each evaluation. Adverse events considered serious will be assessed and recorded until 30 days after discontinuation of study drug, excluding deaths, which will be collected up to 90 days after the first dose of study drug.

The investigator will collect and record all necessary data including investigations that were performed for any AE of special interest, ie, an ischemic abdominal event, ischemic cardiac event, or bronchospasm-related respiratory event.

14.2.1 Laboratory Abnormalities

The investigator will review clinical laboratory test results in a timely fashion. Laboratory abnormalities deemed clinically significant will be recorded as AEs (as defined above) on the eCRF. Those events considered serious should be reported to the sponsor as outlined in Section 14.3.1.

14.2.2 Hospitalizations

Planned hospital admissions and/or planned surgical operations for an illness or disease, which existed before the subject was randomized are not to be considered AEs (eg, re-hospitalization for liver transplantation). However, a baseline condition which deteriorates during the clinical study may be considered an AE.

Following the initial hospital discharge, all re-hospitalizations within 30 days post end of treatment (except for planned hospital admissions or procedures as described above) are to be recorded as a serious AE. Re-hospitalizations will require an investigator assessment and opinion regarding possible recurrence of HRS Type 1.

14.2.3 Complications of the Disease

Complications frequently associated with HRS Type 1 are expected to occur, but should be recorded as an AE or serious AE, as applicable, eg, EVH, hepatic encephalopathy, sepsis, pneumonia, urinary tract infection.

Since HRS Type 1 is the indication under investigation, worsening or aggravation of HRS during the active treatment period (including non-response) will NOT be recorded as a serious AE unless HRS is the cause of death or results in a subsequent re-hospitalization due to suspected recurrence.

14.2.4 Pregnancy

Pregnancy occurring in a subject is NOT considered an AE. However, the investigator must collect pregnancy information for subject and/or subject's partner if the fetus was exposed to the study drug.

14.3 Reporting of Adverse Events/Serious or Unexpected Adverse Reactions or Adverse Events

14.3.1 Site Reporting to Sponsor

Investigators must report all serious AEs to the sponsor (and applicable IRB) whether or not the events are study drug-related or expected. In the event of the death of a subject,

the investigator-reported immediate cause of death will be collected and recorded on the appropriate eCRF page.

All serious AEs must be reported on a serious AE form and faxed to Mallinckrodt within **24 hours** of an investigator becoming aware of the event:

Drug and Device Safety and Pharmacovigilance
Fax: [redacted]
Email: globalpv@mallinckrodt.com

If no fax confirmation received within 1 business day by the reporter, notify Global Pharmacovigilance via phone or email: 800-778-7898 or globalpv@mallinckrodt.com.

The initial serious AE form does not need to be signed by the investigator; however, a signed serious AE form is required within 72 hours of faxing to Mallinckrodt. The initial fax by the investigator will include a detailed description of the event including start and stop dates, causality assessment by the investigator, and supported as needed with written copies of medical records, autopsy reports, and other appropriate documents. Follow-up information (including information requested by the sponsor) should be reported by fax within 24 hours of availability. The investigator is expected to make every effort to collect follow up information for each SAE in a timely fashion after the initial reporting of the SAE.

If there are any specific questions regarding an AE being classified as serious, the investigator should contact the Medical Hotline for this study. The hotline number will be provided in the Site/Investigator Study Manual. Refer to Section 10.9.

If there are any specific questions regarding the completion of the serious AE form, please contact the site monitor.

14.3.1.1 Overdose

In the event of an overdose, the investigator will be required to report this event to the sponsor using a serious AE form, following the SAE reporting timeline.

14.3.1.2 Pregnancy

In the event of pregnancy, the investigator will be required to report this event to the sponsor using the Pregnancy Surveillance Form. Pregnancy should be followed up by the investigator until delivery and the neonatal outcome must be reported.

14.3.2 Site Reporting to Institutional Review Board/Independent Ethics Committee

The investigator must notify the local IRB which approved the trial of the event in accordance with applicable guidelines.

14.3.3 Sponsor Reporting to Regulatory Authorities and Investigators

All reportable AEs, including narrative safety reports of overall findings or data from aggregate analyses, will be reported to the applicable regulatory authorities by the sponsor or designee in accordance to the local regulations as described in the safety review plan for this study. The reporting of serious AEs will be conducted in accordance with ICH E2A (Clinical Safety Data Management: Definitions and Standards for expedited reporting) and regulatory guidelines.

In addition, study endpoints described in Section 6.1 of the protocol that are serious adverse events will only be reported in the final clinical study report unless the event was unusual, unexpected, and there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis).

The sponsor will notify all participating investigators of safety reports, in a blinded fashion, of potential serious risks as described in the safety review plan for this study.

15 Statistical Plan

This is a randomized, double-blind, placebo-controlled, multicenter study of intravenous terlipressin in subjects with HRS Type 1. All subjects who consent to study participation must undergo an in-hospital screening/qualification period of no less than 48 hours prior to enrollment in order to establish the diagnosis of HRS Type 1. Written informed consent will be obtained by the investigator, sub-investigator or qualified designee from the subject or legally-authorized representative prior to the subject qualification form being completed. Qualified subjects are then randomized in a 2:1 ratio to receive either terlipressin or placebo, stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and LVP (at least one single event of at least 4 L or less than 4 L within 14 days prior to randomization). A total of 300 subjects are planned to be enrolled at approximately 70 sites in the United States and Canada.

Randomization will be done centrally using an IXRS stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and pre-enrollment LVP (at least one single event of at least 4 L or less than 4 L within 3 to 14 days prior to randomization). Note, subjects with a LVP of at least 4 L are excluded if it occurs within 2 days prior to randomization (refer to

Section 8.4). Subjects will receive up to 14 days of study drug (maximum 15 days in pre-specified cases, see Section 10.2), administered intravenously 4 times per day.

15.1 Safety Variables

Safety variables will include the following:

- Adverse events.
- Serious adverse events, including deaths.
- Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and SpO_2).
- MELD score.
- Encephalopathy score.
- Laboratory parameters other than SCr.

Adverse events will be collected from the start of study drug administration, during treatment and up to 7 days post end of treatment and at each evaluation. Adverse events considered serious will be collected up to 30 days after the end of treatment. Deaths up to 90 days will be reported as SAEs. Adverse events will be classified by Medical Dictionary for Drug Regulatory Activities (MedDRA) system organ class, preferred term, severity, and seriousness, as well as by the investigator's assessment of the relationship of the AE to the study drug.

15.2 Subject Accounting and Baseline Characteristics

A summary of the study completion status and reasons for discontinuation will be provided for each treatment group. Baseline characteristics (age, gender, race, etc) will be summarized. The number of subjects with medical conditions within each body system will be reported. Summaries of the extent of exposure and protocol deviations will also be provided.

15.3 Statistical Methodology

15.3.1 Sample Size Calculation

[redacted]

Table 15–1: Sample Size Estimates

[redacted]

NOTE: Based on REVERSE, subjects without a known event of pre-enrollment LVP at least 4 L within 2 days of randomization and OT-0401 subjects with baseline SCr no more than 7 mg/dL. SCr values were included while the subjects were on treatment, up to 24 hours after the final dose of study drug. SCr values were excluded after RRT and transplant. If a subject died within 10 days after the reversal, then the subject did not have a reversal. If a subject has an RRT by the 30-day follow-up visit, then the subject did not have a reversal. Three REVERSE terlipressin subjects who achieved a reversal after the 24 hour window were counted as reversals because they would have continued on study drug based on the CONFIRM trial design through the reversal.

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, 200 subjects in the terlipressin group and 100 subjects in the placebo group.

15.3.2 Interim Analysis

An interim analysis will be performed after 50% of the subjects have completed Day 14 or discharge, 150 subjects with approximately 100 in the terlipressin group and 50 in the placebo group. An O'Brien-Fleming spending function is used for the interim analysis alpha spending. For the interim analysis, the methods described in Section 15.3.6.1 will be followed.

15.3.3 Subject Populations

The populations that will be utilized for this study are defined below.

15.3.3.1 Intention to Treat Population

The intention to treat (ITT) population is defined as all randomized subjects. Treatment classification will be based on the randomized treatment. The ITT population defined in this way complies with the ITT principle expressed in ICH E9. This will be the primary population for analysis of efficacy endpoints.

15.3.3.2 Safety Population

The safety population is defined as all randomized subjects who received at least 1 dose of study drug (terlipressin or placebo). Treatment classification will be based on the actual treatment received.

15.3.4 Statistical Analyses

All statistical analyses will be performed and summary tables and data listings will be prepared using SAS® software version 9.2 or higher. All statistical tests will be 2-sided with a final significance level of 0.05, unless stated otherwise. When the assumptions for the planned testing methods do not hold, transformations or nonparametric methods may be employed.

15.3.5 Demographic and Baseline Characteristics

All variables concerning demographic and baseline characteristics will be summarized by treatment group and overall to describe the study population. Continuous variables will be summarized by N, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency and percentage of subjects. The summaries will be presented for all subjects in the safety and ITT populations.

15.3.6 Efficacy Analyses

All efficacy endpoints will be analyzed primarily in the ITT population. Data from the initial treatment course will be utilized in the analyses. Any retreatment courses will be evaluated separately.

15.3.6.1 Primary Efficacy Analysis

Incidence 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). The subject must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine.

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.

Table 15–2 shows the number of subjects with HRS Type 1 reversal that will be needed to achieve success at the interim analysis if the estimate of the placebo rate is accurate (approximately 12.5%).

Table 15–2: Potential Scenarios for Success at the Interim Analysis with a Placebo Rate of Approximately 12.5%

Endpoint	Terlipressin (N = 100) n (%)	Placebo (N = 50) n (%)	Z Score
Scenario 1	34 (34.0)	6 (12.0)	2.8723
Scenario 2	36 (36.0)	7 (14.0)	2.8098

15.3.6.2 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.

If the interim analysis for the primary endpoint is successful then the secondary efficacy analyses will be tested against a corresponding p-value of 0.005166 for a Z score of 2.79651. The p-values from the 4 secondary efficacy analyses will be ordered from largest to smallest and will be compared as in Table 15–3 below:

Table 15–3: Multiple Testing for the Interim Analysis of the Secondary Efficacy Analyses

p-value Ordering	α Comparator	If p-value less than α then:	If p-value at least α then:
Largest p-value	0.005166 = 0.005166/(4 - 4 + 1)	All 4 analyses are significant	Test the second largest p-value
Second largest p-value	0.002583 = 0.005166/(4 - 3 + 1)	The remaining 3 analyses are significant	Test the third largest p-value
Third largest p-value	0.001722 = 0.005166/(4 - 2 + 1)	The remaining 2 analyses are significant	Test the smallest p-value
Smallest p-value	0.001292 = 0.005166/(4 - 1 + 1)	This analysis is significant	No analyses are significant

If the interim analysis for the primary endpoint is not successful then the study will continue onto the final analysis. If the primary efficacy analysis is successful, then the secondary efficacy analyses will be tested against a corresponding p-value of 0.047993 for a Z score of 1.97743, as shown in Table 15–4 below:

Table 15–4: Multiple Testing for the Final Analysis of the Secondary Efficacy Analyses

p-value Ordering	α Comparator	If p-value less than α then:	If p-value ≥ α then:
Largest p-value	0.047993 = 0.047993/(4 - 4 + 1)	All 4 analyses are significant	Test the second largest p-value
Second largest p-value	0.023997 = 0. 047993/(4 - 3 + 1)	The remaining 3 analyses are significant	Test the third largest p-value
Third largest p-value	0.015998 = 0. 047993/(4 - 2 + 1)	The remaining 2 analyses are significant	Test the smallest p-value
Smallest p-value	0.011998 = 0. 047993/(4 - 1 + 1)	This analysis is significant	No analyses are significant

The following are the secondary endpoints:

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value not more than 1.5 mg/dL, while on treatment up to 24 hours after the final dose of study drug, by Day 14 or discharge. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded. HRS reversal will be summarized by treatment group and analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by qualifying SCr (less than 3.4 mg/dL or at least 3.4 mg/dL) and pre-enrollment LVP (at least one single event of at least 4 L or less than 4 L within 3 to 14 days prior to randomization). If the proportion of subjects with HRS reversal is small (expected cell counts less than 5), an unstratified Chi-square test will be used instead of the CMH test. If the number of events per cell is still less than 5, then a Fisher's Exact test will be used.

- Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. HRS reversal is defined as the percentage of subjects with a SCr value not more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). RRT is defined as any procedure to replace non-endocrine kidney function and includes intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis and other dialysis and filtration techniques. The date RRT is instituted for the first time will be used to determine if a subject underwent

RRT by Day 30. This endpoint will be summarized by treatment group and analyzed similarly to HRS reversal.

- Incidence of HRS reversal in the SIRS subgroup, defined as the percentage of SIRS subjects with HRS reversal. HRS reversal is defined as the percentage of subjects with a SCr value not more than 1.5 mg/dL while on treatment by Day 14 or discharge (SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use will be excluded). This endpoint will be summarized by treatment group and analyzed similarly to HRS reversal. The SIRS subgroup is defined as any subject with at least 2 of the following criteria: WBC less than 4,000 or greater than 12,000 cells/μL; HR greater than 90 bpm; temperature greater than 38°C or less than 36°C; respiratory rate of greater than 20/min; HCO_3 less than 21 mmol/L; the latter criterion represents an approximation of the SIRS criterion $PaCO_2$ of less than 32 mm Hg, derived from the observed HCO_3 in subjects with HRS in whom a $PaCO_2$ value was available (from the TAHRS study) and the calculated HCO_3 in subjects with decompensated liver disease and $PaCO_2$ of less than 32 mm Hg.

Incidence of verified HRS reversal without HRS recurrence by Day 30. HRS Type 1 recurrence is defined in Section 10.5. 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 up to 24 hours after the final dose of study drug, by Day 14 or discharge. Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or open-label vasopressor use will be excluded from primary end point analysis. SCr values obtained after midodrine administration will be included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after 17 August 2018. SCr values will also be included if obtained after the administration of a single dose of dobutamine. This endpoint will be summarized by treatment group and analyzed similarly to HRS reversal.

[redacted]

[redacted]

[redacted]

15.3.6.4 Safety Analyses

Continuous variables will be summarized by N, mean, standard deviation, median, minimum and maximum. These include:

- Change from baseline in MELD score.
- Change from baseline in encephalopathy score.
- Change from baseline in BUN.
- Daily values, daily averages, and change from baseline of vital signs of body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, SpO_2, and MAP.
- Change from baseline in laboratory values.

Laboratory shift tables will be created.

Adverse events will be summarized by frequency and percentage of subjects.

15.3.7 Definition of Baseline

For evaluations that are collected at multiple occasions prior to initiation of study drug, the latest non-missing evaluation will be considered the "Baseline" evaluation for analysis. In most cases baseline will be defined as Day 0 of the study period, but a prestudy period value will be utilized instead if the Day 0 value is missing. Study Day 1 will be defined as the first calendar day that study drug is administered during the study period.

15.3.8 Missing Data

Unless otherwise stated, no imputation will be made for missing data.

15.3.9 Procedure for Amendments to the Statistical Plan

It is intended that all statistical analyses specified in this protocol will be performed. However, study observations or analysis results may suggest the need for additional, or changes to the statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report. The statistical plan can be amended and the reasons for amendments will be documented. Furthermore, any additional analyses performed beyond those specified in this protocol will be descriptive in nature and will not include hypothesis testing for the purposes of inferential conclusions.

16 Direct Access, Data Handling, and Record Keeping

16.1 Investigator

The investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to original source data and documents.

All subject information will be recorded on source documents. The eCRFs must be fully completed and include all required data for all subjects enrolled. All eCRF data must be submitted to the sponsor throughout and at the end of the study.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

Any significant changes in study personnel will require an updated Statement of Investigator (eg, FDA Form 1572) to be filed with the sponsor.

The investigator must notify their IRB of protocol violations in accordance with local regulatory and IRB requirements.

16.2 Sponsor

The eCRF data are stored in a database and processed electronically. The sponsor's medical monitor reviews the data for safety information. The data are reviewed for completeness, and logical consistency. Automated validation programs will identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification are forwarded to the study site for resolution.

16.3 Records Retention

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by Good Clinical Practice (GCP) as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

17 Quality Control and Quality Assurance

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the IB, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these study site visits, information recorded in the eCRFs will be verified against source documents.

17.1 Study Monitoring

The sponsor has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the study), the sponsor's monitor will visit the center(s) during the study in accordance with the monitoring plan set forth for this study as well as maintain frequent telephone and written communication. The investigator will permit the sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

17.2 Auditing

The sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

18 Ethics and Responsibility

This study will be conducted in compliance with the protocol, with the sponsor's standard operating procedures and/or guidelines, with the FDA or local regulatory regulations, with the ICH GCP guidelines, and with the Declaration of Helsinki.

18.1 Institutional Review Board/Independent Ethics Committee

This protocol and the written informed consent form shall be submitted to the IRB identified with this responsibility at the research facility. Notification in writing of approval must come from the IRB chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB member, the written approval must indicate such non-participation. The investigator will submit status reports to the IRB at least annually (when applicable). The IRB must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB all changes in research (protocol amendments) and will not make such changes without IRB approval except where necessary to eliminate apparent immediate hazards to human subjects. In these cases, the IRB must be notified within 5 days of the change. The investigator will promptly report to the IRB all unanticipated problems involving risk to subjects or others.
The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB and must agree to share all such documents and reports with the sponsor.

18.1.1 Protocol Amendments

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB and sponsor approval except when necessary

to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB within 5 working days, and submitted to the appropriate regulatory agency in the required time frame.

18.2 Informed Consent

Written informed consent will be obtained from all subjects (or their guardian or legal representative) before any study-related procedures (including any pre-treatment study-specific procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB responsible for approval of this protocol. Each informed consent form shall include the elements required by regulatory regulations in 21 Code of Federal Regulations (CFR) Part 50 and ICH Guidance E6, Section 4.8. The investigator agrees to obtain approval from the sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be kept in the site's regulatory file. A second copy may be filed in the subject's medical record, if allowed by the institution.

18.3 Confidentiality

All information generated in this study will be considered confidential and will not be disclosed to any persons not directly concerned with the study without written prior permission from the sponsor. However, authorized regulatory officials and sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Only initials and/or unique subject numbers in case report forms will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

18.4 Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. After the study ends, the clinical laboratory samples will be destroyed. Bioanalytical samples (ie, plasma, whole blood, urine) for measurement of drug/metabolite content will be retained at a biological storage facility. The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from that sample will still be used for this research.

18.5 Subject Injury

In general, subject to specific provisions in the clinical trial agreement, if a subject is injured as a direct result of an investigational medicinal product, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations.
Where applicable, the sponsor has taken specific national insurance.

18.6 Study Suspension, Termination, and Completion

The sponsor or designee may suspend or terminate the study or part of the study at any time for any reason.

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor or designee and the IRB and provide them with a detailed written explanation. The investigator will destroy all unused (after final drug accountability has been performed) and partially used investigational product per site standard operating procedure. Upon study completion, the investigator will provide the sponsor or designee, IRB, and regulatory agency with final reports and summaries as required by regulations. For IND application studies, or when the data will be used in support of an IND, the investigator must submit a written report to the sponsor or designee and the IRB within 3 months after the completion or termination of the study. Study termination and follow-up will be performed in compliance with applicable standard operating procedures.

18.6.1 Study and Study Site Discontinuation Criteria

The sponsor, investigator, medical monitor or regulatory officials may discover conditions during the study that indicate that the study or study site should be terminated. This action

may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study/study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation or development of the study drug.
- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory regulations.
- Submission of knowingly false information from the study site to the sponsor, study monitor, or regulatory authority.
- Insufficient adherence to protocol requirements
- Study/study site termination and follow-up will be performed in compliance with Mallinckrodt standard operating procedures.

19 Registration of Study and Publication of Data

This study will be registered at the publicly accessible Web site www.clinicaltrials.gov. Registration at other publicly accessible registries will be performed as required.

The results of this study will be published and/or presented at scientific meetings in accordance with usual and customary academic, editorial and ethical practices and requirements.

19.1 Investigator's Ability to Publish

Terms and provisions of publication rights are governed by the Publication Section in the clinical study agreement.

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21 Appendix A: Study IK-4001-HRS-301: Nomogram to Determine the Criterion for SCR Doubling Over a 2-Week Period

The nomogram is intended for use in situations when the SCr value has increased rapidly over a shorter period of time but has not yet doubled within 2 weeks.

To fulfill inclusion criterion #4, subjects must have a rapidly progressive worsening in renal function to a SCr at least 2.25 mg/dL (meeting a trajectory for SCr to double over 2 weeks). The qualifying serum creatinine for subjects on prior vasopressors will be taken after completion of vasopressor washout.

For ease of calculation, these trajectories are estimated by relating a certain required "fold increase in SCr" to the elapsed time in days between 2 measured values (see Figure 3 and Table 21–1); greater proportional increases in SCr are required for observations of shorter duration. As noted in the nomogram, a 1.5-fold increase between the SCr values must be achieved within 4 days of observation. The required fold increase in SCr between SCr values progressively rises from 4 days of observation up to a 2 fold increase by 14 days observation.

Figure 3: Nomogram to Determine the Criterion for SCr Doubling Over a 2-Week Period

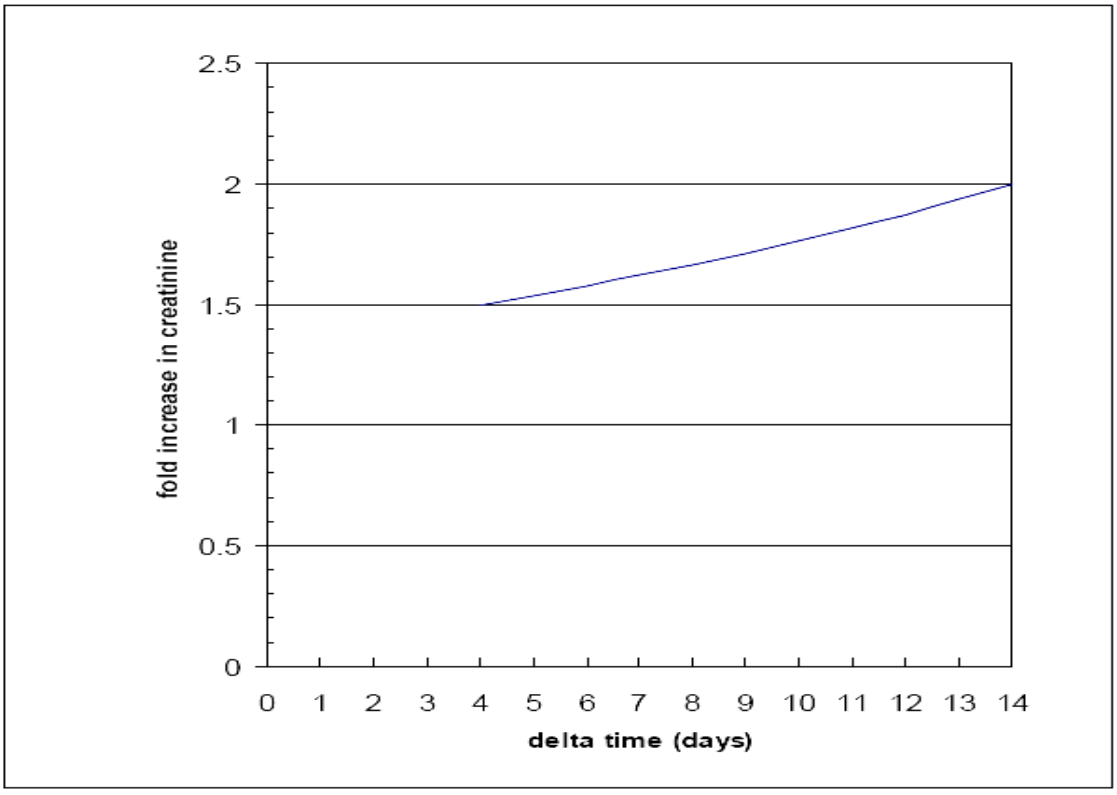

Table 21–1: Elapsed Time in Days and Required Fold Increase in SCr

Elapsed Time (days)	Fold Increase in Creatinine
4	1.50
5	1.54
6	1.58
7	1.62
8	1.67
9	1.71
10	1.76
11	1.82
12	1.88
13	1.94
14	2.00

22 Appendix B: CLIF-SOFA Score

Table 22-1 CLIF-SOFA Score

Supplementary Table 2. CLIF-SOFA Score and Acute on Chronic Liver Failure (ACLF) definitions.

CLIF-SOFA Score*

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dl)	<1.2	≥1.2 - ≤1.9	≥2 - ≤5.9	≥6 - <12	**≥12**
Kidney (Creatinine, mg/dl)	<1.2	≥1.2 - ≤ 1.9	**≥2 - <3.5**	**≥3.5 - <5**	**≥5**
			or requirement for renal-replacement therapy		
Cerebral (HE grade)	No HE	I	II	**III**	**IV**
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	**≥2.5 or platelet count ≤20x10^9/L**
Circulation (MAP, mm Hg)	≥70	<70	**Dopamine ≤5 or Dobutamine or Terlipressin**	**Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1**	**Dopamine >15 or E > 0.1 or NE > 0.1**
Lungs					
PaO2/FiO2 or	>400	>300 - ≤400	>200 - ≤300	**>100 - ≤200**	**≤100**
SpO2/FiO2	>512	>357 - ≤512	>214 - ≤357	**>89 - ≤214**	**≤89**

* Liver failure is defined as serum bilirubin ≥12 mg/dL, kidney failure is defined as serum creatinine ≥2 mg/dL or requirement for renal-replacement therapy, cerebral failure is defined as West Haven score ≥ III or requirement for endotracheal intubation to prevent aspiration pneumonia, coagulation failure is defined as INR (international normalized ratio) ≥2.5 or platelet count ≤20x10^9/L, circulation failure is defined by requirement for vasoactive drugs to maintain hemodynamic stability and respiratory failure is defined as PaO2/FiO2 ≤200 or SpO2/FiO2 ≤214. HE, hepatic encephalopathy; MAP, mean arterial pressure; E, epinephrine; NE, norepinephrine; PaO2, partial pressure of arterial oxygen; FiO2, fraction of inspired oxygen; SpO2,pulse oximetric saturation.

Acute on Chronic Liver Failure (ACLF)

Grade	Organ failure**
No ACLF	This group includes 3 subgroups: (1) No organ failure, (2) patients with a single "non-kidney" organ failure with a serum creatinine <1.5 mg/dl and without hepatic encephalopathy, and (3) patients with single cerebral failure with serum creatinine <1.5 mg/dl
ACLF grade 1	This group includes 3 subgroups: (1) Single kidney failure, (2) patients with single failure of the liver, coagulation, circulation or respiration who had a serum creatinine between 1.5 and 1.9 mg/dl and/or hepatic encephalopathy grade I or II, (3) single cerebral failure who had a serum creatinine between 1.5 and 1.9 mg/dl
ACLF grade 2	Two organ failures
ACLF grade 3	Three organ failures or more

**Organ failure definitions are according to the CLIF-SOFA Score.

Reference: Rodriguez, E; Elia, C; Sola, E; Barreto, R; Graupera, I; Andrealli, A; et al. Terlipressin and Albumin for Type-1 Hepatorenal Syndrome Associated with Sepsis. *J Hepatol.* **2014**, 60, 955-961, supplementary Table 2.