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APPLICATION NUMBER:

022231Orig1s000

INTEGRATED REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Aliza Thompson, Deputy Division Director, DCN Lisa Yanoff, Deputy Office Director, OCHEN
Subject	Summary Review
NDA #	22231
Applicant	Mallinckrodt Pharmaceuticals Ireland Ltd.
Date of Submission	June 9, 2022
PDUFA Goal Date	December 9, 2022
Proprietary Name	Terlivaz
Established or Proper Name	Terlipressin
Dosage Form(s)	Injection, powder for reconstitution
Indication(s)/Population(s)	To improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function. Limitation of Use Patients with a serum creatinine > 5 mg/dL are unlikely to experience benefit.
Action	*Approval*

DCN=Division of Cardiology and Nephrology; OCHEN= Office of Cardiology, Hematology, Endocrinology and Nephrology

Material Reviewed/Consulted	**Names of Discipline Reviewers**
OPQ Integrated Quality Review (August 14, 2022)	Vidya Pai, Sateesh Sathigari, Grafton Adams, and Theodore Carver (Application Technical Lead)

OPQ = Office of Pharmaceutical Quality

On June 9, 2022, Mallinckrodt Pharmaceuticals Ireland Ltd. submitted a complete response to NDA 022231 for Terlivaz (terlipressin) for injection for the treatment of adults with hepatorenal syndrome. This is the third resubmission of the application; the application was previously resubmitted on August 18, 2021, but was not approved because of product quality (facility) deficiencies.[1] As discussed in the OPQ review dated August 14, 2022, the outstanding facility issue has been resolved. Hence, the application will be approved.

[1] See FDA's Integrated Reviews dated September 11, 2020 and February 28, 2022 for additional information on terlipressin's regulatory history and the data supporting efficacy and safety.

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/s/

ALIZA M THOMPSON
09/12/2022 02:46:07 PM

LISA B YANOFF
09/12/2022 02:49:39 PM

Integrated Review of Resubmission

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	22231
Priority, standard, or resubmission	Class 2 resubmission
Submit date(s)	8/18/2021
Received date(s)	8/18/2021
PDUFA goal date	2/18/2022
Division/office	Division of Cardiology and Nephrology
Review completion date	2/17/2022
Established name	terlipressin
(Proposed) trade name	Terlivaz
Pharmacologic class	Vasopressin receptor agonist
Code name	N/A
Applicant	Mallinckrodt
Dose form/formulation(s)	Injection, Lyophilized Powder for solution
Dosing regimen	Initial dose of 0.85 mg every 6 hours on days 1 through 3. Adjust based on changes from baseline in serum creatinine using the dosing chart (dosing chart provided in labeling).
Applicant proposed indication(s)/population(s)	Treatment of hepatorenal syndrome type 1
Proposed SNOMED indication	51292008 |Hepatorenal syndrome (disorder)|
Regulatory action	Complete response
Indication(s)/population(s) (once outstanding product quality issues have been resolved)	To improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function Limitation of Use: Patients with a serum creatinine > 5 mg/dL are unlikely to experience benefit
Approved SNOMED indication	51292008 |Hepatorenal syndrome (disorder)|

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Glossary

ACLF	acute-on-chronic liver failure
AE	adverse event
FDA	Food and Drug Administration
FMQ	FDA MedDRA Query
GI	gastrointestinal
HRS	hepatorenal syndrome
HRS-1	hepatorenal syndrome type 1
ISS	integrated summary of safety
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
NDA	new drug application
RD	risk difference
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SMQ	Standardised MedDRA Query
SPA	Special Protocol Assessment

I. Executive Summary

1. Summary of Regulatory Action

On August 18, 2021, Mallinckrodt Hospital Products, Inc. submitted a complete response to NDA 022231 for Terlivaz® (terlipressin) for injection for the treatment of adults with hepatorenal syndrome Type 1 (HRS-1). The regulatory action will be Complete Response due to Product Quality issues (facilities deficiency). Otherwise, there are no deficiencies precluding approval.

Background

HRS-1 is a rare and serious disease associated with significant morbidity and mortality. There are currently no FDA-approved treatments for HRS. The only definitive treatment for HRS is liver transplantation in those with chronic liver disease. Terlipressin is a synthetic, 12-amino-acid peptide analog of vasopressin that has twice the selectivity for vasopressin V_1 receptors as compared with V_2 receptors. Terlipressin differs from endogenous vasopressin by the substitution of lysine for arginine at the 8th position and the addition of three glycyl residues at the amino terminus.

Terlipressin's regulatory history is summarized in FDA's Integrated Review, dated September 11, 2021. In brief, the NDA was originally submitted to FDA in May 2009 and received a Complete Response (CR) because of insufficient evidence supporting efficacy and safety for the intended use. On March 12, 2020, the Applicant submitted a complete response to the 2009 CR Letter. The submission was based on the results of a randomized, double-blind, trial comparing intravenous (IV) terlipressin to placebo in 300 adult patients with HRS-1 (CONFIRM). The trial met its primary endpoint of "verified HRS reversal;" however, safety findings in the trial, and in particular, a greater incidence of serious adverse events of respiratory failure in the terlipressin as compared to the placebo arm raised concern that the risks of terlipressin might outweigh its benefits. Given these findings, the FDA convened an Advisory Committee Meeting to discuss the application and obtain input on whether the application should be approved. Committee members generally agreed that CONFIRM met its primary endpoint but also felt that respiratory failure and fluid overload were serious risks associated with use of terlipressin and that a clear and effective risk mitigation strategy would be needed to ensure the product's benefits outweighed its risks. When asked to vote on whether terlipressin should be approved for the treatment of HRS-1, eight Committee members voted "Yes" and seven members voted "No."

On September 11, 2020, the FDA issued a CR letter, citing the greater incidence of serious adverse events (SAEs) of respiratory failure in the terlipressin as compared to the placebo arm in CONFIRM and concern that the risks of terlipressin might outweigh its benefits, particularly given unresolved questions about the clinical significance of the primary endpoint. In its letter, the FDA acknowledged the Applicant's proposed mitigation strategy, but noted that it had not been prospectively tested and that it was unclear whether its implementation would adversely impact terlipressin's efficacy for the proposed use. To address the concern, the FDA stated that

the Applicant would need to conduct an adequate and well-controlled study that demonstrated an acceptable benefit-risk profile, perhaps utilizing the risk mitigation strategy proposed by the Applicant.

Interactions with Applicant following issuance of 2020 Complete Response Letter

Following issuance of the 2020 Complete Response Letter, the FDA met with the Applicant on several occasions to discuss a path forward. At the End of Review meeting held on October 26, 2020, the FDA reiterated its concern that the proposed risk mitigation strategy for respiratory failure was developed retrospectively based on findings in CONFIRM and had not been prospectively tested. The FDA further noted that the plan included subjective elements that could be challenging to implement in practice. In response, the Applicant proposed a revised risk mitigation strategy limited to objective (as opposed to subjective) pre-treatment criteria. The FDA indicated that it was open to considering the Applicant's proposal for a risk mitigation strategy based on objective pretreatment variables and post-hoc analyses of trial data, but also voiced concern about adopting a strategy that had not been prospectively tested. To address this issue, the FDA suggested that the Applicant conduct additional analyses that could provide further confidence the proposed strategy effectively mitigates risk, as well as reassurance that terlipressin provides a benefit when used within the context of such a strategy.

At a follow-up meeting on January 29, 2021, the Applicant provided additional analyses to support the proposed mitigation strategy. The FDA acknowledged the challenges associated with conducting an additional adequate and well-controlled trial, but also noted that it was not clear that the existing data would be sufficient to determine that terlipressin, when used in the context of the proposed risk mitigation strategy, would provide an acceptable risk-benefit profile. The FDA indicated, however, that it might be possible to use the existing data to support such a determination in a more narrowly defined population in whom it might be reasonable to accept a greater degree of uncertainty. At a subsequent meeting on May 4, 2021, the Applicant proposed a more narrowly defined "Mitigated Population" in whom there might be greater assurance of net benefit; the FDA agreed that the proposed population appeared reasonable and encouraged the Applicant to move forward with the resubmission of their application.

Proposed Mitigation Strategy

The Applicant's mitigation strategy is based on three objective criteria, which are identified prior to treatment initiation (baseline). These criteria are intended to mitigate the risk of serious respiratory failure and/or enhance the clinical risk-benefit profile of terlipressin treatment. Each of the mitigation criteria is described below, along with a summary of the Applicant's rationale for its inclusion (see the Appendix for further discussion).

Criteria:

1. ACLF Grade 3 [1]: In CONFIRM, patients with the most severe liver failure (ACLF Grade 3 at baseline) had a greater risk of SAEs (30% vs. 0%) and death (23% vs. 0%) due to

[1] Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of cirrhosis, defined multiple organ failure(s), and high short-term mortality. The Chronic Liver Failure-Sequential Organ Failure

respiratory failure when treated with terlipressin compared to placebo. Patients with ACLF Grade 3 at baseline also did not appear to benefit from terlipressin as indicated by a similar incidence of verified HRS reversal in the terlipressin and placebo arms (18% vs. 17%, respectively).

2. Serum creatinine (SCr) ≥ 5 mg/dL: In CONFIRM, the predicted probability of verified HRS reversal with terlipressin steadily decreased with increasing baseline serum creatinine. Terlipressin-treated patients with the most advanced renal failure (defined by the Applicant as a SCr ≥ 5 mg/dL at baseline) were less likely than patients with a SCr < 5 mg/dL to achieve verified HRS reversal (32% vs. 9%, respectively), though there still appeared to be some differential benefit compared with placebo (9% vs. 0%). Terlipressin-treated patients with a SCr 5 ≥ mg/dL at baseline also had a numerically higher incidence of mortality up to Day 90 compared to placebo (61% vs. 43%).
3. Patients listed for transplant with a MELD score of ≥ 35[2] : Transplant-listed patients with a MELD score of ≥ 35 are most likely to receive an imminent liver transplant, definitive treatment for HRS-1, and therefore represent a population whose ability to receive a transplant may be negatively impacted by adverse effects of terlipressin.

Application of Mitigation Criteria to CONFIRM

To support the use of the proposed criteria, the Applicant submitted the results of post-hoc efficacy and safety analyses of CONFIRM using the "Mitigated Population" (i.e., patients who were randomized in CONFIRM who do not meet any of the aforementioned criteria). The Mitigated Population included 132 patients in the terlipressin group and 71 patients in the placebo group. In contrast, the ITT Population, defined as all randomized patients with at least one baseline assessment, included 199 patients in the terlipressin group and 101 in the placebo group.

The primary and secondary endpoint efficacy findings in the Mitigated Population were generally consistent with the findings in the ITT Population. In the Mitigated Population, 48/132 patients in the terlipressin arm (36%) as compared to 13/71 in the placebo arm (18%) achieving verified HRS reversal (nominal $p = 0.007$). As in the ITT Population, the proportion of patients who initiated renal replacement therapy was also numerically lower in the terlipressin as compared to the placebo arm in the Mitigated Population. These findings provide reassurance of efficacy in the Mitigated Population.

As would be expected given the objective of the mitigation strategy, the risk of serious or fatal respiratory failure in patients on terlipressin compared with placebo was considerably reduced in the Mitigated Population (10% vs. 7%, Risk Difference of 3%) compared to that in the overall CONFIRM Safety Population (14% vs. 5%, Risk Difference of 9%). Excluding patients with ACLF Grade 3, a significant risk factor for respiratory failure in the CONFIRM study,

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Assessment Score (CLIF-SOFA) is often used to define the nature and severity of associated organ failures and assess prognosis in patients with ACLF.

[2] The Model for End-stage Liver Disease (MELD) score is a prognostic scoring system for patient with serious liver disease. A MELD cutoff of ≥ 35 has been used to prioritize patients who are at highest risk of dying while awaiting liver transplantation and therefore, directs livers to those most in need.

contributed primarily to the observed reduction. Available data, as well as biologic plausibility, also suggest that oxygen saturation monitoring using pulse oximetry can be used to mitigate the risk of respiratory failure.

Summary and Conclusions

The CONFIRM trial, an adequate and well-controlled trial, demonstrated that terlipressin improves kidney function in adults with HRS with rapid reduction in kidney function, an effect on kidney function that is likely to translate into a favorable effect on the need for renal replacement therapy over the short-term.[3] Clinical studies previously conducted by the Applicant in patients with HRS-1 provide confirmatory evidence of effectiveness. Terlipressin can cause serious or fatal respiratory failure and ischemic events, adverse reactions that may make a patient ineligible for liver transplant, if listed. Although the mitigation strategy for the risk of respiratory failure has not been prospectively tested, it is reasonable to believe that this risk can be effectively mitigated by close monitoring of a patient's respiratory status, including monitoring of oxygen saturation, and avoiding use in patients who are at significant risk of respiratory failure. Limiting use to a more narrowly defined population (i.e., avoiding use in patients with high prioritization for liver transplantation and those with markedly elevated serum creatinine levels) also provides greater assurance of an acceptable benefit-risk profile. As such, the review team recommends approval once the outstanding Product Quality issues have been resolved.

Postmarketing Requirements and Risk Evaluation and Mitigation Strategy (REMS)

At this time, there are no postmarketing requirements or commitments. The review team agrees that a REMS is not needed to help ensure that the benefits of the product outweigh its risks; the agreed-upon labeling is considered sufficient.

II. Clinical and Statistical Assessment

2. Overview of CONFIRM

In brief, CONFIRM was a randomized, double-blind, placebo-controlled trial comparing intravenous (IV) terlipressin to placebo in adult patients with HRS-1. The trial, which was conducted under a Special Protocol Assessment Agreement, enrolled 300 patients who were randomized 2:1 to terlipressin or placebo, administered as a 1 mg IV bolus injection every 6 hours for a maximum of 14 days. CONFIRM met its primary endpoint with 58/199 patients in the terlipressin arm (29%) compared to 16/101 patients in the placebo arm (16%) achieving

[3] For further discussion of the primary endpoint in the trial and the data supporting its use as a surrogate, see FDA's Integrated Review, dated September 11, 2021.

verified HRS reversal[4] (p=0.012). The exploratory efficacy analyses suggested a trend in improvement for renal replacement treatment (RRT)-free survival in the terlipressin arm but did not suggest a mortality benefit. There was a greater incidence of serious adverse event (SAE) of "respiratory failure" on terlipressin compared to placebo (14% vs 5%, respectively). Sixty-one percent of these events (17/28) in the terlipressin arm resulted in death, while one fatal respiratory failure event was reported in the placebo arm (1/5, 20%). It is thought that the increased clinical use of albumin for HRS in recent years may exacerbate hypervolemia and the additional fluid load associated with albumin use may have contributed to the observed incidence and severity of respiratory failure events in terlipressin-treated patients in CONFIRM; however, the underlying mechanism remains unclear.

3. Efficacy Evaluation

See FDA's Integrated Review, dated September 11, 2021, for a discussion of the efficacy findings in CONFIRM. The analyses that follow focus on the efficacy findings in the "Mitigated Population."

The Mitigated Population (defined as all randomized patients but excluding patients with baseline acute-on-chronic liver failure Grade 3, baseline serum creatinine ≥ 5 mg/dL, and patients listed for transplant at baseline with baseline MELD ≥ 35) included 132 subjects in the terlipressin group and 71 patients in the placebo group. In contrast, the ITT Population, defined as all randomized patients with at least one baseline assessment, included 199 patients in the terlipressin group and 101 in the placebo group.

3.1. Demographic, Baseline Characteristics and Patient Disposition

As shown in Table 14 in the appendix, key baseline demographic and clinical characteristics in the Mitigated Population were similar in the two treatment groups.

In both the ITT and Mitigated Population missing data were low: all patients had complete data to ascertain whether or not they achieved verified HRS reversal, and no major differences were observed between treatment groups in the disposition of patients through Day 90. The primary reason for discontinuation from the study was death in both treatment groups in both the ITT and Mitigated Population (Table 15 in the appendix).

[4] Verified HRS reversal was defined as 2 consecutive serum creatinine values ≤ 1.5 mg/dL at least 2 hours apart, while on treatment, by Day 14 or discharge. In order to be counted in the primary endpoint, patients also needed to be alive without renal replacement therapy for at least 10 days after achieving verified HRS reversal.

3.2. Primary Analysis

The primary efficacy endpoint in CONFIRM was the incidence of verified HRS reversal, defined as percentage of subjects with two consecutive SCr values ≤1.5mg/dL at least 2 hours apart while on treatment by Day 14, or discharge (on treatment was defined as up to 24 hours after the final dose of study drug). In addition, subjects had to be alive without RRT for at least 10 days after achieving verified HRS reversal.

As shown in table below, the primary efficacy endpoint findings in the Mitigated Population were consistent with the findings in the ITT Population.

Table 2. Primary Endpoint, Verified HRS Reversal, CONFRIM

	ITT Population		Mitigated Population	
	Placebo (N=101)	**Terlipressin (N=199)**	**Placebo (N=71)**	**Terlipressin (N=132)**
Verified HRS reversal[1], n (%)	16 (16%)	58 (29%)	13 (18%)	48 (36%)
Z score[2]	2.53		2.68	
p-value[2]	0.012		0.007	

Source: results for ITT Population were from FDA review of the 21Feb2020 resubmission. Results for Mitigated Population was verified by FDA statistical reviewer.
[1] Defined as two consecutive serum creatinine (SCr) values ≤1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge (on treatment was defined as up to 24 hours after the final dose of study drug). Subjects had to be alive without renal replacement therapy (RRT) for at least 10 days after achieving verified HRS reversal. SCr values after RRT, trans jugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressor
[2] See calculation details in Appendix III.5.

3.3. Secondary Analyses

The statistical analysis plan for CONFIRM specified four secondary endpoints that were to be tested using the Hochberg procedure to control the overall type 1 error rate. Like the primary endpoint, these endpoints assessed treatment effects on HRS reversal, such as the durability of the response. Secondary endpoint findings for the Mitigated Population and ITT Population are shown in the table below. As shown in the table, efficacy findings in the subset were generally consistent with the findings in the ITT Population.

Table 3. Secondary Endpoints, CONFRIM

	ITT Population			Mitigated Population		
	Placebo N=101 (n(%))	**Terlipressin N=199(n(%))**	**p-value**	**Placebo N=71 (n(%))**	**Terlipressin N=132 (n(%))**	**Nominal p-value**
Incidence of patients with HRS reversal[1] while on treatment[2] by Day 14 or discharge	17 (17)	72 (36)	<0.001	13 (18)	59 (45)	<0.001
Percentage of subjects with HRS reversal without RRT to Day 30 ("Durability of HRS reversal")	16 (16)	63 (32)	0.003	13 (18)	51 (39)	0.003
Incidence of HRS reversal in the SIRS subgroup while on treatment by Day 14 or discharge	N=48 3 (6)	N=84 28 (33)	<0.001	N=30 1 (3)	N=51 21 (41)	<0.001
Incidence of verified HRS reversal without HRS recurrence by Day 30	16 (16)	48 (24)	0.092	13 (18)	38 (29)	0.103

Source: Study Report Tables 28, 29, 30, 31, Study Report Addendum Table 15.
1 HRS reversal defined as one SCr value ≤1.5 mg/dL. Serum creatinine values after RRT, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressor were excluded
2 On-treatment defined as up to 24 hours after the final dose of study drug
Abbreviations: HRS, hepatorenal syndrome; RRT, renal replacement therapy

3.4. RRT-Free Survival

During the prior review cycle, the Applicant and FDA conducted exploratory analyses to assess treatment effects on clinical outcomes associated with HRS and/or thought to be predicted by treatment effects on kidney function. As discussed in FDA's Integrated Review dated September 9, 2021, these exploratory analyses suggested a trend for improvement in RRT-free survival, (defined as alive and without RRT until Day 90) in the terlipressin arm, but did not suggest an all -cause mortality benefit in the ITT population. As shown in Table 4, the proportion of patients who initiated RRT was numerically lower in the terlipressin as compared to placebo arm in the Mitigated Population, consistent with the findings in the ITT Population.

Table 4. Summary of Initiation of RRT and/or Death to Day 90, by Treatment Arm, CONFRIM

	ITT Population			Mitigated Population		
	Placebo N=101 (n(%))	Terlipressin N=199(n(%))	p-value	Placebo N=71(n(%))	Terlipressin N=132 (n(%))	Nominal p-value
RRT-free survival	28 (28)	67 (34)	0.09[1]	22 (31)	51 (39)	0.09[1]
RRT initiation or death	73 (72)	132 (66)	0.09[1]	49 (69)	81 (61)	0.09[1]
RRT initiation	39 (39)	58 (29)	0.07[2]	24 (34)	36 (27)	0.26[2]
Death without preceding RRT	34 (34)	74 (37)	0.64[2]	25 (35)	45 (34)	0.73[2]
All-cause Death[3,4]	47 (47)	103 (52)	0.5[1]	33 (46)	59 (45)	0.6[1]

Source: FDA analysis, dataset tte1
1 P-value from log rank test
2 (Gray 1988)
3 An information request (16Jun2020) was sent to the Applicant related to discrepancies in the number of deaths by treatment arm in different datasets/tables. Per the Applicant, the tte1 dataset includes deaths after database lock, which were not included in the adae dataset
4 One subject on placebo who died by Day 90 did not receive study treatment, but was included in the ITT analysis
Abbreviations: ITT, intent-to-treat; RRT, renal replacement therapy

4. Safety Evaluation

See FDA's Integrated Review, dated September 11, 2021, for a discussion of the safety findings in CONFIRM. The analyses that follow focus on the safety findings in the Mitigated Population as compared to the CONFIRM Safety Population.

The Mitigated Population used in safety analyses excluded 68 patients (34%) on terlipressin and 28 patients (28%) on placebo who met the proposed objective mitigation criteria in the safety population. The most common reason for exclusion was an ACLF Grade of 3 at baseline (Table 5).

Table 5 Reasons for Exclusion from the Mitigated Population, CONFIRM (Safety Population)

Mitigated criteria[1]	Placebo (N=28)	Terlipressin (N=68)	Total (N=96)
ACLF Grade 3	18 (64.3)	40 (58.8)	58 (60.4)
ACLF Grade 3 only	14 (50.0)	28 (41.2)	42 (43.8)
ACLF_3 and SCr	0	5 (7.4)	5 (5.2)
ACLF_3 and Transplant-listed with MELD ≥35	4 (14.3)	7 (10.3)	11 (11.5)
SCr ≥ 5	7 (25.0)	23 (33.8)	30 (31.2)
SCr ≥ 5 only	6 (21.4)	15 (22.1)	21 (21.9)
SCr and ACLF_3	0	5 (7.4)	5 (5.2)
SCr and Transplant-listed with MELD ≥35	1 (3.6)	3 (4.4)	4 (4.2)
Transplant-listed with MELD ≥35	8 (28.6)	20 (29.4)	28 (29.2)
Transplant-listed with MELD ≥35 only	3 (10.7)	10 (14.7)	13 (13.5)
ACLF_3 and Transplant-listed with MELD ≥35	4 (14.3)	7 (10.3)	11 (11.5)
SCr and Transplant-listed with MELD ≥35	1 (3.6)	3 (4.4)	4 (4.2)

[1]Patients could have more than one mitigated criterion
Source: Reviewer's table

4.1. Deaths

As previously noted, the purpose of the proposed mitigation strategy was to identify a more narrowly defined population in whom the risk of serious respiratory failure would be adequately mitigated and the beneficial effect of terlipressin was likely to be preserved. In the CONFIRM Safety Population, all-cause mortality up to 90 days from the start of treatment was higher in the terlipressin arm as compared to the placebo arm (51% vs. 44%, respectively).[5] In the Mitigated Population, all-cause mortality up to 90 days was similar in the two arms (Table 6). As would be expected given the objective of the mitigation strategy, the incidence of AEs leading to death due to respiratory failure was reduced in the terlipressin arm in the Mitigated Population as compared with the Safety Population. The risk difference between the arms in the incidence of fatal respiratory failure events in the Safety Population was 8.0% compared to 4.7% in the Mitigated Population; otherwise the risk difference between arms for other common AEs that led to deaths was similar in the Mitigated Population and Safety Population.

Table 6 Death up to day 90, CONFIRM, Safety and Mitigated Populations

	Safety Population		Mitigated Population	
	Placebo (N=99)	Terlipressin (N=200)	Placebo (N=71)	Terlipressin (N=132)
Total Death	44 (44.4)	102 (51.0)	32 (45.1)	61 (46.2)
Hepatic disorder (SMQ, narrow)	27 (27.3)	49 (24.5)	18 (25.4)	33 (25.0)
Acute respiratory failure/respiratory failure	1 (1.0)	18 (9.0)	1 (1.4)	8 (6.1)
Multiple organ dysfunction syndrome	5 (5.1)	11 (5.5)	3 (4.2)	5 (3.8)
septic shock/shock	2 (2.0)	11 (5.5)	1 (1.4)	7 (5.3)
sepsis/sepsis syndrome	0	5 (2.5)	0	2 (1.5)
Acute renal failure (SMQ, narrow)	0	4 (2.0)	0	4 (3.0)
Gastrointestinal hemorrhage (SMQ, narrow)	0	6 (3.0)	0	4 (3.0)

Source: Reviewer's table

The timing of deaths is shown in Table 7. In the Safety Population, the incidence of death was similar in the two arms by Day 7 and was numerically higher in the terlipressin arm compared with the placebo arm at all time points of interest beyond Day 7. In contrast, in the Mitigated Population, the incidence of death was numerically lower in the terlipressin arm than in the placebo arm through Day 60 and similar in the treatment arms by Day 90.

Table 7 Timing of Death up to Day 90, CONFIRM, Safety and Mitigated Population

	Safety Population		Mitigated Population	
	Placebo (N=99)	Terlipressin (N=200)	Placebo (N=71)	Terlipressin (N=132)

[5] Mortality data presented in this section reflect adverse events that led to death up to 90 days from the start of treatment as reported on the Adverse Event Case Report Forms.

	Safety Population		Mitigated Population	
	Placebo (N=99)	Terlipressin (N=200)	Placebo (N=71)	Terlipressin (N=132)
Death during study treatment period	1 (1.0)	9 (4.5)	1 (1.4)	4 (3.0)
Death by Day 7	11 (11.1)	22 (11.0)	8 (11.3)	9 (6.8)
Death by Day 14	24 (24.2)	53 (26.5)	16 (22.5)	25 (18.9)
Death by Day 30	36 (36.4)	78 (39.0)	26 (36.6)	42 (31.8)
Death by Day 60	41 (41.4)	94 (47.0)	30 (42.3)	53 (40.2)
Death by Day 90[a]	44 (44.4)	102 (51.0)	32 (45.1)	61 (46.2)
Days from start of study drug to death				
Mean (SD)	19 (17.3)	22 (19.7)	20 (17.59)	26 (21.8)
Median (Min, Max)	12 (3, 81)	14 (2, 81)	14 (3, 81)	20 (2, 81)

a. Included two deaths in CONFIRM without a date of death
Source: Reviewer's table

4.2. Serious Adverse Events

The incidence of SAEs was slightly higher in the terlipressin arm as compared to the placebo arm in the CONFIRM Safety Population and similar in the two arms in the Mitigated Population. There was a numerically lower incidence of SAEs due to respiratory failure in the Mitigated Population as compared with the Safety Population among terlipressin-treated patients (Table 8). In addition, the absolute risk difference of such SAEs in patients on terlipressin compared with placebo was considerably lower in the Mitigated Population (2.8%) compared to that in the overall CONFIRM Safety Population (8.3%). As shown in Table 8, there were no other obvious differences between the two populations in the incidence of other frequently reported SAEs.

Table 8 Serious Adverse Events up to Day 30, CONFIRM, Safety and Mitigated Population

	Safety Population		Mitigated Population	
	Placebo (N=99)	Terlipressin (N=200)	Placebo (N=71)	Terlipressin (N=132)
Any SAE	60 (60.6)	130 (65.0)	42 (59.2)	81 (61.4)
Hepatic disorders (SMQ)	33 (33.3)	50 (25.0)	23 (32.4)	31 (23.5)
Acute respiratory failure/respiratory failure	5 (5.1)	27 (13.5)	5 (7.0)	13 (9.8)
Sepsis/sepsis shock	0	14 (7.0)	0	8 (6.1)
Gastrointestinal hemorrhage (SMQ)	4 (4.0)	17 (8.5)	3 (4.2)	11 (8.3)
Abdominal pain/vomiting	1 (1.0)	14 (7.0)	1 (1.4)	9 (6.8)
Haemodynamic oedema, effusions and fluid overload (SMQ)	2 (2.0)	10 (5.0)	2 (2.8)	6 (4.5)
Intestinal ischemia	0	2 (1.0)	0	1 (0.8)

Source: Reviewer's table

4.3. Pulse Oximetry

In the CONFIRM study, oxygen saturation (SpO_2) and fraction of inspired oxygen (FiO_2) were to be assessed at baseline and once daily while patients were on therapy. To assess whether monitoring oxygenation could mitigate the risk of respiratory failure, the applicant assessed whether patients with respiratory SAEs had a reported SpO_2 value of <90% and/or an FiO_2 of ≥ 0.36 at least 1 day prior to the onset of respiratory failure.

Among patients in the Mitigated Population, 7 out of 13(54%) with SAEs of respiratory failure in the terlipressin arm had an SpO_2 (n=2) or FiO_2 (n =5) value meeting the selected criteria, at least 1 day prior to the onset of respiratory failure (3 at baseline and 4 during treatment). Among terlipressin treated patients who did not report a SAE of respiratory failure (n =119), only 3 patients (2.5%) met the SpO2 or FiO2 criteria. Similar results were observed in the Safety Population, with 11 out of 27 patients (41%) with respiratory failure SAEs in the terlipressin arm having an SpO_2 or FiO_2 value below the aforementioned threshold at least 1 day prior to the onset of respiratory failure (7 at baseline and 4 during treatment). In contrast, only 8 out of 173 patients (4.3%) who did not have a respiratory failure SAE met the threshold for SpO_2 or FiO_2. These results suggest that daily oxygen saturation monitoring using pulse oximetry may be useful to mitigate risk of respiratory failure.

III. Appendices

5. Applicant's Rationale for Components of Mitigation Strategy

5.1. ACLF Grade 3

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of cirrhosis, defined multiple organ failure(s), and high short-term mortality[1]. The Chronic Liver Failure-Sequential Organ Failure Assessment Score (CLIF-SOFA) is often used to define the nature and severity of associated organ failures and assess prognosis in patients with ACLF[2]. The scoring system has 4 grades (0-3), with ACLF Grade 3 defined as 3 or more failing organ systems.

In post-hoc subgroup analyses of CONFIRM, the incidence of SAEs of respiratory failure and fatal respiratory failure was greater in patients with ACLF Grade 3 at study baseline than in patients with ACLF Grade ≤ 2 at baseline (Table 9).

Table 9 Incidence of Overall and Respiratory Failure SAEs, by ACLF Status at Baseline, Safety Population, CONFIRM Study

	ACLF Grade (0-2)		ACLF Grade 3		Total	
	Placebo (N=81)	Terlipressin (N=160)	Placebo (N=18)	Terlipressin (N=40)	Placebo (N=99)	Terlipressin (N=200)
Any SAE	48 (59.3)	98 (61.3)	12 (66.7)	32 (80.0)	60 (60.6)	130 (65.0)
Respiratory failure SAE	**5 (6.2)**	**15 (9.4)**	**0**	**12 (30.0)**	**5 (5.1)**	**28 (14.0)**
Fatal respiratory failure	**1 (1.2)**	**8 (5.0)**	**0**	**9 (22.5)**	**1 (1.0)**	**17 (8.5)**

Source: Reviewer's analysis, dataset: adsl, adae & agrp.
Abbreviations: SAE, serious adverse event; ACLF, acute-on-chronic liver failure

In addition, post-hoc analyses suggested that patients with ACLF Grade 3 at baseline experienced little to no differential benefit over placebo with regard to HRS reversal in CONFIRM (Table 10).

Table 10 Verified HRS Reversal by Baseline ACLF Grade, ITT Population, CONFIRM Study

	Terlipressin		Placebo	
Baseline ACLF Grade	**N**	**n (%)**	**N**	**n (%)**
Grade ≤ 2	159	51 (32.1)	83	13 (15.7)
Grade 3	**40**	**7 (17.5)**	**18**	**3 (16.7)**

Source: Table 2 in CONFIRM CSR Addendum

The Applicants hypothesizes that because terlipressin cannot sufficiently reduce the marked arterial vasodilation in patients with ACLF Grade 3, it may further impair left ventricular function, increase cardiac afterload, or increase pulmonary vascular resistance in these patients, placing them at greater risk of pulmonary edema and respiratory failure.

5.2. Baseline Serum Creatinine ≥ 5 mg/dL

According to the Applicant, the selection of a serum creatinine (SCr) ≥ 5 mg/dL as one of the mitigation criteria was to improve the overall benefit-risk profile of terlipressin by avoiding use of terlipressin in a subgroup of patients less likely to benefit from terlipressin and more likely to experience AEs, including AEs leading to death, and lower survival. Although the degree of kidney failure, as measured by SCr, did not appear to be associated with a greater risk of respiratory failure in CONFIRM, post-hoc analyses suggested that patients with higher levels of SCr may derive less benefit from terlipressin. The Applicant also asserts that the overall safety profile in patients with SCr ≥ 5 mg/dL was also not favorable to terlipressin. The Applicant reasons that a threshold of SCr ≥ 5 mg/dL is clinically relevant and consistent with the cutoff value for the highest grade of kidney organ failure in the CLIF-SOFA ACLF grade schema.

In CONFIRM, 30 patients had a baseline SCr ≥ 5 mg/dL (n =23 in the terlipressin arm and n = 7 in the placebo arm). As shown in the table below, few patients with a baseline SCr ≥ 5 mg/dL achieved HRS reversal (Table 11).

Table 11 Verified HRS Reversal by Baseline Serum Creatinine Category, ITT Population, CONFIRM

	Terlipressin		Placebo	
Baseline SCr	**N**	**n (%)**	**N**	**n (%)**
< 5 mg/dL	176	56 (31.8)	93	16 (17.2)
≥ 5 mg/dL	**23**	**2 (8.7)**	**8**	**0 (0.0)**

Source: Table 7 in CONFIRM CSR Addendum

Severe AEs and AEs leading to death in patients with SCr ≥ 5 mg/dL were numerically greater in the terlipressin arm as compared to the placebo arm (Table 12) in CONFIRM; though no notable differences were observed in terms of SAEs by SCr category.

Table 12 Overview of Safety Data by Baseline Serum Creatinine Category, Safety Population, CONFIRM

	Baseline SCr < 5 mg/dL		Baseline SCr ≥ 5 mg/dL	
	Terlipressin N=177 n (%)[a]	**Placebo N=92 n (%)[a]**	**Terlipressin N=23 n (%)[a]**	**Placebo N=7 n (%)[a]**
All adverse events	**155 (87.6)**	**82 (89.1)**	**21 (91.3)**	**6 (85.7)**
Severe adverse events	72 (40.7)	36 (39.1)	12 (52.2)	2 (28.6)
Serious adverse events	113 (63.8)	55 (59.8)	17 (73.9)	5 (71.4)
Respiratory failure[a]	25 (14.1)	5 (5.4)	2 (8.7)	0 (0.0)
Adverse events leading to death up to 30 days post-treatment	**71 (40.1)**	**38 (41.3)**	**12 (52.2)**	**2 (28.6)**

[a] Respiratory failure includes respiratory failure and acute respiratory failure.

Source: Table 8 in CONFIRM CSR Addendum

Overall survival was numerically lower in patients on terlipressin compared to placebo, regardless of baseline SCr category; however, the numerical difference in overall survival estimate was particularly notable in the subset of patients with a SCr ≥ 5 mg/dL. For patients with SCr ≥ 5 mg/dL, the overall survival estimate through Day 90 was 39% for terlipressin and 50% for placebo.

Table 13 Overall Survival up to 90 Days by Baseline SCr Category, CONFIRM, ITT Population

	Baseline SCr ≥ 5 mg/dL					Baseline SCr < 5 mg/dL				
	Terlipressin		Placebo			Terlipressin		Placebo		
	N	Parameter	N	Parameter	p-value[a]	N	Parameter	N	Parameter	p-value[a]
Overall Survival up to 90 Days										
Survival Estimate	23	0.383	8	0.500	.408	176	0.504	93	0.544	.650
Median Days of Survival	23	28.0	8			176		93		
Alive at Day 90 (n, %)	23	9 (39.1)	8	4 (50.0)		176	90 (51.1)	93	52 (55.9)	

[a] The p-value comparing the survival estimates is from a two-sample log rank test.
N = number of subjects in the study and treatment group. n = number of subjects in the category of subjects in the study and treatment group.
Source: CONFIRM CSR Listings 16.2.1.3.1, 16.2.6.6.1, 16.2.6.7.1

Source: Table 14.2.4.12 in CONFIRM CSR Addendum

FDA Comment: While the rationale proposed by the Applicant appears reasonable, it is important to note that the incidence of terlipressin-related SAEs was not increased among patients with SCr ≥ 5 mg/dL; the numerically greater incidence of SAEs leading to death was

largely due to other SAEs related to the underlying disease (e.g., hepatic disorder). As such, it's not clear that terlipressin played a role. Overall, there was no strong evidence supporting that the safety profile of terlipressin is considerably worse in this subset.

5.3. Transplant-listed patients with MELD ≥35

At a Type A meeting held on January 29, 2021, the FDA acknowledged the challenges associated with conducting an additional adequate and well-controlled trial, but also noted that it was not clear that the existing data would be sufficient to determine that terlipressin, when used in the context of the proposed risk mitigation strategy, would provide an acceptable risk-benefit profile. The FDA indicated, however, that it might be possible to use the existing data to support such a determination in a more narrowly defined population and, as a starting point for the discussion, raised the issue of further narrowing the population to patients who were ineligible for a transplant. The FDA noted that liver transplant was the definitive therapy for patients with cirrhosis and HRS-1 who otherwise have a high risk of death over weeks to months; therefore, a drug-related toxicity that could render a patient ineligible for transplant, either temporarily or permanently, was of particular concern for transplant-eligible patients. The FDA also noted that an improvement in kidney function and avoidance of dialysis may represent a greater benefit to patients who are not transplant-eligible, and, therefore, have limited therapeutic options.

In response to the FDA's suggestion, the Applicant proposed to further narrow the intended population to exclude patients based on MELD score, a score used to prioritize patients for liver transplant. Specifically, the Applicant proposed to exclude transplant-listed patients with a MELD score of ≥ 35, since this population was felt to be more likely to receive an imminent liver transplant.

6. Efficacy: Additional Information and Assessment

6.1. Calculation of primary endpoint

According to FDA's Integrated Review, dated September 11, 2021, the Z-score for the primary endpoint is based on the difference in proportions of subjects with events.

$$\frac{\hat{p}_1 - \hat{p}_0}{\sqrt{\hat{p}_{pool}(1-\hat{p}_{pool})\left\{\frac{1}{n_0}+\frac{1}{n_1}\right\}}}$$

where $n_0 = 71$, $n_1 = 132$, $\hat{p}_0 = \frac{13}{71}$, $\hat{p}_1 = \frac{48}{132}$, $and\ \hat{p}_{pool} = \frac{13 + 48}{71 + 132}$.

6.2. Additional tables

Table 14. Baseline Demographics and Clinical Characteristics

	ITT Population		Mitigated Population	
	Terlipressin (N = 199)	Placebo (N = 101)	Terlipressin (N = 132)	Placebo (N = 71)
Age (yr)				
N	199	101	132	71
Mean (SD)	54.0 (11.34)	53.6 (11.83)	55.6 (10.77)	54.1 (12.09)
Median	54.7	54.5	56.8	54.6
Min, max	23.2, 78.0	30.6, 81.6	28.1, 78.0	31.7, 81.6
Sex (n,%)				
Male	120 (60.3)	59 (58.4)	78 (59.1)	41 (57.7)
Female	79 (39.7)	42 (41.6)	54 (40.9)	30 (42.3)
Ethnicity (n,%)				
Hispanic or Latino	32 (16.1)	13 (12.9)	18 (13.6)	10 (14.1)
Not Hispanic or Latino	165 (82.9)	88 (87.1)	112 (84.8)	61 (85.9)
Race (n,%)				
American Indian or Alaskan Native	2 (1.0)	0 (0.0)	1 (0.8)	0 (0.0)
Asian	5 (2.5)	1 (1.0)	2 (1.5)	0 (0.0)
Black or African American	12 (6.0)	5 (5.0)	6 (4.5)	3 (4.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	177 (88.9)	94 (93.1)	120 (90.9)	67 (94.4)
Baseline serum creatinine (mg/dL)				
Mean (SD)	3.5 (1.01)	3.5 (1.06)	3.2 (0.68)	3.3 (0.79)
Median	3.3	3.3	3.1	3.2
Min, max	2.3, 6.9	2.1, 6.2	2.3, 4.9	2.1, 4.9

[Source: Applicant's table in study report addendum, verified by FDA reviewer]

Table 15. Summary of Reason for Discontinuation of Study

	ITT Population			Mitigated Population		
	Terlipressin (N = 199) n (%)	Placebo (N = 101) n (%)	Total (N = 300) n (%)	Terlipressin (N = 132) n (%)	Placebo (N = 71) n (%)	Total (N = 203) n (%)
Completed study through follow-up/Day 90 Visit						
Yes	87 (43.7)	52 (51.5)	139 (46.3)	66 (50.0)	36 (50.7)	102 (50.2)
No	112 (56.3)	49 (48.5)	161 (53.7)	66 (50.0)	35 (49.3)	101 (49.8)
Primary reason for noncompletion of study through to follow-up/Day 90 Visit						
Adverse event	101 (50.8)	45 (44.6)	146 (48.7)	61 (46.2)	32 (45.1)	93 (45.8)
Death	101 (50.8)	45 (44.6)	146 (48.7)	61 (46.2)	32 (45.1)	93 (45.8)
Other adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	4 (2.0)	2 (2.0)	6 (2.0)	0 (0.0)	1 (1.4)	1 (0.5)
Subject lost to follow-up	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other[a]	6 (3.0)	2 (2.0)	8 (2.7)	5 (3.8)	2 (2.8)	7 (3.4)

[Source: Applicant's table in study report addendum]

7. Labeling Summary of Considerations

The following key labeling considerations were discussed and implemented in the course of the review.

Under Indications and Usage;

The indication statement was refined to optimize the benefit- risk balance of the therapy in the indicated population (see discussion under Section 5.2).

Under Dosage and Administration;

Methodology regarding Acute-on-Chronic Liver Failure assessment has been included in the prescribing information via reference included in Section 15; (*Jalan R, et al; Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014 Nov;61(5):1038-47.)*

Instructions to monitor patients for hypoxia using continuous pulse oximetry has been included, in various appropriate locations in the prescribing information.

Under Contraindications;

Contraindications for patients experiencing hypoxia or worsening respiratory symptoms, and for patients with ongoing coronary, peripheral or mesenteric ischemia.

Under Warnings and Precautions;

A warning indicating that the benefits of TERLIVAZ may not outweigh its risks in patients with high prioritization for liver transplantation has been included.

8. Postmarketing Requirements and Commitments

None.

9. References

1. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61:1038-47.
2. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic Liver Failure is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis. Gastroenterology. 2013; 144 (7):1426-37.
3. Gray, RJ, 1988, A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk, The Annals of Statistics, 16(3):1141-1154.

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Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	22231
Priority, standard, or resubmission	Class 2 resubmission
Submit date(s)	3/12/2020
Received date(s)	3/12/2020
PDUFA goal date	9/11/2020
Division/office	Division of Cardiology and Nephrology
Review completion date	See DARRTS electronic signature page
Established name	terlipressin
(Proposed) trade name	Terlivaz
Pharmacologic class	Vasopressin Receptor Agonist
Code name	Not known
Applicant	Mallinckrodt
Dose form/formulation(s)	Injection, Lyophilized Powder for solution
Dosing regimen	Initial dose of 1 mg every 6 hours
Applicant proposed indication(s)/population(s)	Treatment of hepatorenal syndrome type 1
Proposed SNOMED indication	51292008 |Hepatorenal syndrome (disorder)|
Regulatory action	Complete response
Approved indication(s)/population(s) (if applicable)	Not Applicable
Approved SNOMED indication	51292008 |Hepatorenal syndrome (disorder)|

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Glossary

ACLF	acute-on-chronic liver failure
AE	adverse event
ARDS	acute respiratory distress syndrome
BiPAP	bilevel positive airway pressure
BP	blood pressure
CI	confidence interval
CLIF-SOFA	Chronic Liver Failure–Sequential Organ Failure Assessment
CRF	case report form
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
FDA	Food and Drug Administration
FMQ	FDA MedDRA Query
GI	gastrointestinal
HR	heart rate
HRS	hepatorenal syndrome
HRS-1	hepatorenal syndrome type 1
HRS-2	hepatorenal syndrome type 2
ICU	intensive care unit
IQR	interquartile range
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
K-M	Kaplan-Meier
LVP	large volume paracentesis
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
MODS	multiple organ dysfunction syndrome
NDA	new drug application
RD	risk difference
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SIRS	systemic inflammatory response syndrome
SMQ	Standardised MedDRA Query
SPA	Special Protocol Assessment
TIPS	transjugular intrahepatic portosystemic shunt
V_1 receptor	vasopressin receptor 1
V_2 receptor	vasopressin receptor 2

I. Executive Summary

1. Summary of Regulatory Action

On February 21, 2020, Mallinckrodt Hospital Products IP Limited submitted a complete response to NDA 022231 for Terlivaz® (terlipressin) for injection for the treatment of adults with hepatorenal syndrome Type 1 (HRS-1). Terlipressin is a synthetic, 12-amino-acid peptide analog of vasopressin that differs from endogenous vasopressin by the substitution of lysine for arginine at the 8th position and the addition of three glycyl residues at the amino terminus. The NDA was originally submitted to FDA in May 2009 but received a Complete Response (CR) because of insufficient evidence supporting efficacy and safety for the intended use.

Regulatory history

In support of the original NDA, the Applicant submitted the results of two clinical trials: OT-0401 and TAHRS. OT-0401 was a randomized, placebo-controlled, double-blind study in 112 patients with HRS-1. TAHRS was a smaller, open-label study in 46 patients (out of a planned 100) with HRS-1 and HRS-2. The primary endpoint in OT-0401, the trial that provided principal support for efficacy, assessed changes in renal function (the per-protocol primary endpoint was "treatment success" at Day 14, defined as the percentage of patients alive with serum creatinine ≤1.5 mg/dL on at least 2 measurements 48±2 hours apart).

Using the prespecified endpoint and analytic plan, the OT-0401 results were not statistically significant. The safety database supporting approval was also small and considered to be insufficient to support safety for the intended use. Moreover, important serious adverse events tended to occur more frequently, or earlier, in terlipressin-treated patients, compared to patients in the respective control groups.

In its CR Letter, FDA stated that the Applicant would need to conduct at least one additional adequate and well-controlled study to demonstrate the efficacy and safety of intravenous terlipressin for the treatment of HRS-1. To address this requirement, the Applicant conducted a third, somewhat larger (196 patients) randomized, placebo-controlled, double-blind trial in patients with HRS-1 (REVERSE); however, the prespecified primary endpoint, which assessed effects on renal function, did not reach statistical significance. The Applicant then conducted a fourth, larger trial— CONFIRM. The Applicant's class 2 resubmission is based on the results of this trial.

Overview of CONFIRM

In brief, CONFIRM was a randomized, double-blind, placebo-controlled trial comparing intravenous (IV) terlipressin to placebo in adult patients with HRS-1. The trial, which was conducted under a Special Protocol Assessment Agreement, enrolled 300 patients who were randomized 2:1 to terlipressin or placebo, administered as a 1-mg IV bolus injection every

6 hours for a maximum of 14 days. The prespecified primary endpoint was the incidence of verified HRS reversal, defined as 2 consecutive serum creatinine values ≤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). In order to be counted in the primary endpoint, patients also needed to be alive without renal replacement therapy (RRT) for at least 10 days after achieving verified HRS reversal.

Efficacy Findings

The trial met its primary endpoint with 58/199 patients in the terlipressin arm (29%) as compared to 16/101 patients in the placebo arm (16%) achieving verified HRS reversal (p=0.012). Although the Agency agreed to this endpoint, the data supporting its use as a surrogate for adverse outcomes associated with HRS-1 are limited. As noted in prior FDA memos, ideally, one would want the development program to show an improvement in an outcome, however, concerns about the feasibility of showing such an effect, bearing in mind that terlipressin is not targeting the underlying cause of HRS (i.e., the disease in the liver) and the rarity of the condition, led to its acceptance. Arguably, one can also draw parallels to the Division's approach with other "supportive" therapies, such as pressors for the treatment of hypotension. Thus, the concept was to "support the patient" until the underlying cause of the condition could be successfully remedied via some other means. Moreover, to bolster that efficacy findings, the Division attempted to build a safeguard into the trial ─ we communicated to the Applicant that in addition to meeting the primary endpoint, we would also expect to see favorable trends on outcomes thought to be associated with HRS or thought to be predicted by treatment effects on kidney function.

To address this issue, the Applicant provided the results of exploratory analyses for outcomes in CONFIRM including renal replacement therapy (RRT)-free survival, outcomes following liver transplant, and length of intensive care unit (ICU) stay. In brief, the analyses suggest a trend in improvement for RRT-free survival in the terlipressin arm. The results with respect to mortality were, however, not reassuring; the proportion of patients who died was numerically slightly greater on terlipressin than on placebo. Analyses of outcomes following liver transplant in patients who received a liver transplant are challenging to interpret, largely because such analyses are based on a post-randomization variable. Finally, as discussed in the body of this review, the Applicant's exploratory analyses on ICU stay are difficult to interpret and are not compelling for a variety of reasons. We maintain that evidence of favorable effects on outcomes thought to be associated with HRS would have provided reassurance of efficacy; however, in retrospect, such an expectation may not have been reasonable, given that failure to observe a positive trend does not exclude there being a favorable effect.

Safety

FDA's safety evaluation focused on the data obtained in CONFIRM and the known and potential toxicities of terlipressin based on its mechanism of action, the larger experience with the pharmacologic class (vasopressin receptor agonist) and terlipressin's post-marketing experience in other countries. As discussed in the body of the review, there was a greater incidence of serious adverse events of "respiratory failure" on terlipressin than in the placebo arm (14% vs 5%, respectively), a finding that was unexpected because there was no signal for respiratory

failure in OT-0401. These serious respiratory events tended to occur soon after administration of terlipressin, with more than half of these events occurring within 5 days of initiating the drug. Close to seventy percent of the cases in the terlipressin group required intubation, and, of those who were not intubated, the majority received comfort care and died shortly after the event. It is thought that with increasing use of albumin for HRS in recent years, hypervolemia may become more pronounced, and may have contributed to the higher incidence and severity of respiratory failure in terlipressin-treated patients in CONFIRM. However, the mechanism remains uncertain. The Applicant has proposed a risk mitigation plan; however, we have concern about the ability of the proposed strategy to mitigate risk adequately because of difficulty with implementation (some elements of the proposed plan are subjective) and because the strategy has not been prospective tested. There are also outstanding questions regarding whether implementation of the proposed strategy might reduce terlipressin's efficacy as a treatment for HRS.

Treatment-emergent adverse-events (AEs) in CONFIRM were otherwise generally consistent with the established safety profile of terlipressin based on the drug's mechanism of action and the findings observed in prior trials. In brief, there was a greater incidence of treatment-emergent AEs in the terlipressin arm than in the placebo arm for expected risks including ischemia-associated events, respiratory events, gastrointestinal (GI) events, and bradycardia. In addition, edema and fluid overload-related AEs were reported by more patients on terlipressin than in the placebo arm. More patients in the terlipressin arm also reported SAEs of serious infections – mainly sepsis and septic shock. Mortality up to Day 90 was also numerically greater on terlipressin than in the placebo arm as noted above.

Summary and Conclusions

Although the trial met is primary endpoint, safety findings in CONFIRM, and in particular, the greater incidence of serious adverse events of respiratory failure in the terlipressin as compared to the placebo arm (14% vs 5%, respectively) raise concern that the risks of terlipressin may outweigh its benefits, particularly given unresolved questions about the clinical significance of the primary endpoint. The Applicant has proposed a risk mitigation strategy; however, the strategy has not been prospectively tested, and it is unclear whether its implementation would adversely impact terlipressin's efficacy for its proposed use.

Applicant's Path Forward

The Applicant will need to conduct an adequate and well-controlled study that demonstrates an acceptable risk-benefit profile, perhaps utilizing the proposed risk mitigation strategy. The primary endpoint and analytic plan should be discussed with and agreed upon by the Division prior to initiation. Given the data proffered thus far, we believe a two-sided p-value of 0.1 could provide sufficient reassurance that the risk mitigation strategy does not adversely impact the product's efficacy.

We acknowledge there are outstanding questions about the clinical significance of a primary endpoint based on changes in creatinine, especially if it must be balanced against serious risks. However, available data suggest that terlipressin's effect on renal function in CONFIRM likely translates into a favorable effect on the need for renal replacement therapy.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HRS is a serious condition that can develop in patients with acute or chronic liver disease with advanced hepatic failure and portal hypertension. HRS is thought to result from reduced renal perfusion, stemming from arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension. • Hepatorenal syndrome (HRS) is one of many causes of acute kidney injury in patients with acute or chronic liver disease and is a diagnosis of exclusion. HRS is considered to be a "functional" form of acute kidney injury in which the kidneys themselves are not structurally damaged. Historically, HRS has been categorized as Type 1 and Type 2 based upon the rapidity of rise in and absolute level of serum creatinine (SCr).[1] Hepatorenal syndrome type 1 (HRS-1) is associated with poor survival, with 1-month mortality rates of 40-70%. Prognosis is even more dismal for patients who require renal replacement therapy. • HRS is considered to be a rare disease, although the exact incidence is unknown. In the largest prospective study of patients with cirrhosis and ascites published thus far, HRS developed in 18% of patients at one year and 39% at five years.	HRS-1 is a rare and serious disease associated with significant morbidity and mortality.
Current Treatment Options	• The only definitive treatments for HRS are liver transplantation in those with chronic liver disease and recovery of liver function in those with an acute and reversible cause of liver disease. • There are no FDA-approved therapies for the treatment of HRS, although a number of interventions are used in clinical practice in an attempt to reverse the impairment in kidney function, such as albumin and off-label pharmacologic interventions (e.g., midodrine, octreotide, norepinephrine, vasopressin). • Terlipressin has been approved for HRS-1 in several countries outside of the United States.	There are currently no FDA-approved treatments for HRS. There is limited evidence for the efficacy and safety of current standard of care, which includes albumin and off-label pharmacologic interventions.Therefore, there is an unmet medical need for FDA-approved therapies to reduce morbidity and mortality in patients with HRS-1.

[1] In recent years, the community has moved away from this categorization of HRS and guidelines currently recommend staging based on a modified version of the Kidney Disease: Improving Global Outcomes (KDIGO) staging system for acute kidney injury.

Benefit	• The effectiveness of terlipressin on HRS-1 was evaluated in a double-blind, placebo-controlled trial in 300 patients with HRS-1 who were randomized 2:1 to receive terlipressin or placebo1-2 mg intravenously every 6 hours for a maximum of 14 days. The primary endpoint in the trial was the incidence of "verified HRS reversal," defined as two consecutive serum creatinine values ≤1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge, whichever came first (on treatment defined as up to 24 hours after the final dose of study drug). Patients needed to be alive without renal replacement therapy (RRT) for at least 10 days after achieving "verified HRS reversal." • The trial met its primary endpoint. The proportion of patients with "verified HRS reversal" was statistically significantly greater in the terlipressin as compared to the placebo arm (29% vs. 16%, respectively, p=0.012). Sensitivity analyses were consistent with the primary efficacy endpoint finding. • Subgroup analyses raise questions about differential efficacy in patients with and without alcoholic hepatitis and in patients with and without SIRS at baseline. It is unclear, however, whether these differences are based on biological differences, or instead represent play of chance. • To better understand the clinical significance of the primary endpoint, exploratory analyses were conducted to assess treatment effects on the following clinical outcomes associated with HRS and/or thought to be predicted by treatment effects on kidney function: RRT initiation and/or survival, outcomes post-liver transplant, and length of intensive care unit (ICU) stay. In brief: - RRT-free survival was slightly greater for terlipressin as compared to placebo (34% vs. 28%, respectively). However, terlipressin was not associated with improved overall survival (48% terlipressin vs 53% placebo). - The proportion of patients who initiated RRT after receiving a liver transplant was lower in the terlipressin as compared to the placebo group (20% vs. 45%, respectively). However, this analysis is challenging to interpret, mainly because it is based on a post-randomization variable. - The mean length of ICU stay was shorter in the terlipressin arm as compared to the placebo arm (6.4 days and 13.5 days, respectively). However, this analysis is challenging to interpret for a variety of reasons.	FDA accepted "verified HRS reversal", a putative surrogate endpoint, as the primary endpoint for CONFIRM given the challanges of studying clinical outcomes in patients with HRS-1. Although FDA agreed to this endpoint, during discussions of the trial, it also stated that should the trial succeed on the primary endpoint, it would expect favorable trends in clinical outcomes thought to be predicted by successfully treating HRS- 1. The submitted data demonstrate that terlipressin impresses kidney function over the short-term in patients with HRS-1. Exploratory analyses suggest a trend in improvement for RRT-free survival in the terlipressin arm, but do not suggest a mortality benefit. Treatment effects on post-transplant RRT-free survival and ICU length of stay are challenging to interpret.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Compared to placebo, terlipressin demonstrated statistically significant treatment effects on prespecified secondary endpoints of HRS reversal while on treatment (36% vs. 17%, respectively), HRS reversal without RRT to Day 30 (32% vs. 16%, respectively), and HRS reversal in the SIRS subgroup while on treatment (33% vs. 6%, respectively), but not on “verified HRS reversal” without HRS recurrence by Day 30 (24% vs 16%, respectively).	

Risk and Risk Management	• FDA's safety evaluation focused on the data obtained in CONFIRM and the known and potential toxicities of terlipressin based on its mechanism of action, the larger experience with the pharmacologic class (vasopressin receptor agonist) and terlipressin's post-marketing experience in patients with HRS-1 in countries where terlipressin is marketed. In CONFIRM, a total of 299 subjects received at least one dose of study drug (n = 200 and 99 in the terlipressin and placebo group, respectively). Additional supportive safety data are provided by the previous two phase 3 studies. • A greater incidence of treatment-emergent adverse events was reported on terlipressin versus placebo for the expected risks including: – Ischemia-associated events (4.5% vs. 0%) – Respiratory events (40% vs. 25%) ▪ Respiratory failure (18% vs. 10%) ▪ Dyspnoea (13% vs. 5%) – Gastrointestinal (GI) events (48% vs. 35%) ▪ Abdominal pain (21% vs. 8%) ▪ Diarrhea (13% vs.7%) ▪ Nausea (16% vs. 10%) – Edema/fluid overload (28% vs. 16%) – Bradycardia (5% vs. 0%) • A greater incidence of serious adverse events (SAEs) was reported on terlipressin vs. placebo for respiratory failure (14% vs. 5%), sepsis/septic shock (7% vs. 0%), abdominal pain/vomiting (7% vs. 1%), edema/fluid overload (5% vs. 2%) and ischemic events (1% vs. 0). • Mortality up to Day 90 was greater in the terlipressin group as compared to the placebo group (51% vs. 44%). • The increased risk of serious respiratory failure is a significant safety concern. Review of the data indicates that: – These serious respiratory events tended to occur soon after administration of terlipressin, with the majority of these events occurring on treatment and more than half of these events occurring within 5 days of initiating terlipressin. – These SAEs were associated with significant morbidity and mortality. Close to 70% of the cases in the terlipressin group required intubation. Of those who were not intubated, the majority received	The greater incidence and severity of serious respiratory failure events in the terlipressin as compared to placebo arm is a significant safety concern. It is possible that with increasing use of albumin for HRS in recent years, hypervolemia may become more pronounced, and may have contributed to the higher incidence and severity of respiratory failure in terlipressin-treated patients in CONFIRM. An increased risk of sepsis was also seen but the mechanistic basis for this risk is not clear. Other safety findings were generally consistent with the known safety profile of terlipressin and expected risks based on the drug's mechanism of action and the safety findings observed in prior trials. The majority of the known risks appear manageable. However, ischemic and respiratory events could lead to serious or fatal outcomes. The Applicant's risk mitigation plan for respiratory failure was developed retrospectively, based on findings in the CONFIRM study, and it is unclear whether the proposed measures will adequately mitigate risk or whether implementation of these measures could also diminish efficacy. There are also elements of the proposed plan that may be challenging to implement clinically. Thus the effects of these measures are questionable and difficult to estimate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	comfort care and died shortly after the event. The fatality of these serious events in the terlipressin group was 61% (17/28) compared to 20% (1/5) in the placebo group. – It is possible that the additional fluid load associated with albumin use in recent years may have contributed to the observed incidence and severity of respiratory failure events in terlipressin-treated patients in the CONFIRM study. It is plausible that terlipressin could increase the risk of respiratory failure and fluid overload via its effects on vasopressin receptors V1a and/or V2. However, given the medical complexities in these patients and possible multiple causes of respiratory failure, it is challenging to determine how terlipressin may have contributed to these events. The potential role of albumin use and fluid overload complicate the clinical presentation and management of these respiratory events. • The Applicant's risk mitigation plan was developed retrospectively, based on findings in the CONFIRM study: – Treatment with terlipressin in patients with acute-on-chronic liver failure (ACLF) Grade 3 would not be not recommended. – Treatment with terlipressin in patients with a baseline serum creatinine (SCr) ≥ 5 mg/dL would not be not recommended. – Additional proposed clinical mitigation steps include: ▪ Terlipressin should not be administered in patient with clinical features of pulmonary edema, pneumonia, hepatic encephalopathy ≥ Grade 3, or new onset or worsening dyspnea or tachypnea until these events are addressed and resolved. ▪ Management of fluid overload during treatment with terlipressin (this strategy was implentmented in CONFIRM). ▪ Terlipressin should be interrupted immediately in the setting of treatment-emergent pulmonary edema, new onset or worsening pneumonia, and unresolved hepatic encephalopathy ≥ Grade 3 with risk of aspiration.	

Conclusions Regarding Benefit-Risk

Although the CONFIRM trial met its primary endpoint, safety findings in the trial and in particular, the greater incidence of serious adverse events of respiratory failure in the terlipressin as compared to the placebo arm (14% vs 5%, respectively) raise concern that the risks of terlipressin may outweigh its benefits for the proposed use. To better understand this issue, we considered the important potential benefits and risks of terlipressin, including clinical outcomes possibly predicted by verified HRS reversal, treatment effects on liver transplant, and serious adverse events thought to be related to terlipressin (see Table 3). The confidence intervals around these potential benefits and risks are wide, indicating substantial uncertainty in these estimates, thus limiting the ability to weigh terlipressin's benefits against its risks. We acknowledge that the Applicant has proposed a risk mitigation strategy; however, the strategy has not been prospectively tested and it is unclear whether its implementation would adversely impact terlipressin's efficacy for its proposed use.[2]

We conclude that the application cannot be approved. The findings in CONFIRM raise concern that terlipressin's risks outweigh its benefits, particularly given outstanding questions about the clinical significance of the primary endpoint. Although the Applicant has proposed a risk mitigation strategy, the strategy has not been prospectively tested and it is unclear whether its implementation would adversely impact terlipressin's efficacy for its proposed use.

Table 3. Potential Key Benefits and Risks for Overall Study Population in CONFIRM

Benefits		Risks	
Benefits	**Treatment Effect (%) Terlipressin vs. Placebo (95% CI)**	**Risks (Through 30 Days After Last Dose)**	**Risk Difference (%) Terlipressin vs. Placebo (95% CI)**
"Verified HRS reversal" (putative surrogate endpoint)	13 (3, 24)	Any SAEs of interest	21 (13, 30)
Clinical outcomes possibly predicted by surrogate (Day 90)		Respiratory failure SAEs	9 (2, 15)
Alive	-5 (-18, 8)	Sepsis/septic shock SAEs	7 (4, 11)
No RRT	10 (-3, 22)	Abdominal pain/vomiting SAEs	6 (2, 9)
Alive post-liver transplant	7 (-5, 19)	Edema/fluid overload SAEs	3 (-1, 7)
No RRT post-liver transplant	25 (1, 50)	Ischemia-related SAEs	1 (-0.4, 2)
Liver transplant (among patients listed at any point (Day 90)	-21 (-40, -2)		

Source: Reviewer analysis
Abbreviations: RRT, renal replacement therapy; SAE, serious adverse event; HRS hepatorenal syndrome; CI, confidence interval

[2] FDA conducted a hypothesis-generating analysis to explore the potential impact of the objective mitigation criteria proposed by the Applicant on risk mitigation and benefit-risk; however, the results of this analysis are challenging to interpret given the retrospective application of the criteria to the trial finding and the fact that the criteria were derived in part based on analyses of the trial data. See Appendix section III.19.1 for details.

II. Interdisciplinary Assessment

3. Introduction

Disease Background

Hepatorenal syndrome (HRS) is a serious condition that can develop in patients with acute or chronic liver disease with advanced hepatic failure and portal hypertension. HRS is thought to be caused by vasodilatation in the splanchnic circulation, leading to renal vasoconstriction and a decrease in urine output, with an acute increase in serum creatinine (a marker of kidney function). The condition is considered a diagnosis of exclusion and, historically, has been divided into more and less severe phenotypes (HRS-1 and hepatorenal syndrome type 2 (HRS-2), respectively) based upon the rapidity of the rise in, and absolute level of serum creatinine.

HRS, and in particular HRS-1, is associated with poor survival, with 1-month mortality rates of 40-70% reported in the setting of cirrhosis (Fede et al. 2012). The only definitive treatments for HRS are liver transplantation in those with chronic liver disease and recovery of liver function in those with an acute and reversible cause of liver disease. There are no approved therapies for HRS, although a number of interventions are used in clinical practice in an attempt to reverse the impairment in kidney function.

Regulatory History

Terlipressin is a synthetic, 12-amino-acid peptide analog of vasopressin that differs from endogenous vasopressin by the substitution of lysine for arginine at the 8th position and the addition of three glycyl residues at the amino terminus. A U.S. marketing application for terlipressin was originally submitted to FDA for the treatment of HRS-1 in May 2009. Principal support for the proposed indication was provided by OT-0401, a double-blind, placebo-controlled study in 112 patients with HRS-1.

The per-protocol primary endpoint was “treatment success” at Day 14, defined as the percentage of patients alive with serum creatinine ≤1.5 mg/dL with at least two measurements 48±2 hours apart. Using the prespecified primary endpoint and the original analytic plan, the results of the trial were not statistically significant. In November 2009, FDA issued a complete response letter indicating that the application could not be approved because of insufficient evidence supporting efficacy and safety for the intended use. FDA indicated that to address this issue, at least one additional adequate and well-controlled study was needed to demonstrate the efficacy and safety of terlipressin for the treatment of HRS-1.

FDA further stated that such a study would need to be successful, using prespecified endpoint(s) and analytic plan, at $p<0.05$. To address this requirement, the applicant conducted the REVERSE trial in ~200 patients with HRS-1. As in the first trial, the point estimate for the primary endpoint (in this case, confirmed HRS reversal defined as two serum creatinine values of ≤ 1.5 mg/dL at least 48 hours apart, on treatment, and without intervening renal replacement therapy or liver

transplant) was favorable; but failed to reach statistical significance. The Applicant then conducted the CONFIRM trial, the focus of this review.

Identified Review Issues

- Effects on clinical outcomes thought to be predicted by HRS reversal
- Respiratory failure

3.1. Approach to the Review

This was a joint review. Rekha Kambhampati and John Lawrence focused on the data supporting efficacy, and Tzu-Yun McDowell focused on the data supporting safety.

Table 4. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations[1] for Terlipressin

Study Identifier	Study Population	Study Design	Regimen (Number. Treated), Duration	Primary Endpoint	Number of Subjects Randomized	Number of Centers and Countries
MNK19013058 (CONFIRM)*	HRS-1 with cirrhosis and ascites	All three: phase 3, multicenter, randomized, placebo-controlled, double blind	IV terlipressin1-2 mg Q6H; max 14/15 d; both groups received standard of care albumin	Verified HRS reversal and alive without RRT at Day 10[2]	N 300 (199 terlipressin, 101 placebo)	60 in 2 countries (USA (55), Canada (5))
REVERSE	HRS-1		IV terlipressin1-2 mg Q6H; max 15/16 d; both groups received albumin 20-40 g/d as clinically indicated	Confirmed HRS reversal[3]	N 196 (97 terlipressin, 99 placebo)	52 in 2 countries (USA (majority), Canada)
OT-0401	HRS-1		IV terlipressin 1-2 mg Q6H; max 14 d; both groups received albumin 100 g on Day 1 and then 25 g/d	HRS reversal with treatment success at Day 14 (i.e., no RRT or recurrence of HRS)[4]	N 112 (56 terlipressin, 56 placebo)	35 in 3 countries (USA (30), Russia (3), Germany (2))

Source: Applicant
*This Integrated Review focuses primarily on the results of the CONFIRM study
[1] Includes all submitted phase 3 clinical studies, even if not reviewed in-depth
[2] Verified HRS reversal was defined as subjects with two consecutive serum creatinine (SCr) values ≤1.5 mg/dL at least 2 hours apart, on treatment. Subjects also had to be alive without RRT 10 days after achieving verified HRS reversal.
[3] Defined as subjects with two SCr values of ≤1.5 mg/dL at least 48 hours apart, on treatment, and without intervening RRT or liver transplant
[4] HRS reversal was defined as SCr ≤1.5 mg/dL, with at least two measurements 48±8 hours apart. Treatment success defined as achieving HRS reversal and not requiring RRT or having recurrence of HRS at Day 14. Of note, the time window for the collection of the two SCr measurements to determine HRS reversal was amended from 48±2 hours to 48±8 hours late in the trial.
Abbreviations: HRS, hepatorenal syndrome; HRS-1, hepatorenal syndrome type 1; N, number of subjects; Q, every; H, hours; g, grams; d, day(s); IV, intravenous; RRT, renal replacement therapy

4. Patient Experience Data

No patient experience data were collected during the CONFIRM trial or submitted as part of the application.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: Perspectives shared at Advisory Committee Meeting	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Synthetic vasopressin analogue
Mechanism of action	Terlipressin is a synthetic vasopressin analog derived from lysine-vasopressin. It is a systemic vasoconstrictor selective to vasopressin V_1 vascular receptors. Lysine-vasopressin is the active metabolite of terlipressin and it also acts selectively on the vasopressin V_1 vascular receptors. In patients with HRS-1, the V_1 receptor-mediated vasoconstrictor activity of terlipressin, particularly in the splanchnic area, results in an increase in effective arterial volume, an increase in mean arterial pressure (MAP), and normalization of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system) resulting in increased renal blood flow.
Active moieties	Both terlipressin and lysine-vasopressin (active metabolite of terlipressin) selectively act on the V_1 vascular receptors. Terlipressin is a synthetic 12-amino acid peptide. It differs from endogenous human vasopressin by the substitution of lysine for arginine at the eighth position of the endogenous molecule (Lys^8) and the addition of three glycyl residues at the amino terminus. Lysine-vasopressin is the pharmacologically active metabolite of terlipressin. Terlipressin has about 1% of the V_1 receptor activity compared to lysine-vasopressin.
Molecular weight	Terlipressin has a molecular mass of 1227.28 daltons (as a free base).
QT prolongation	Terlipressin does not prolong the QTc interval to any clinically relevant extent.
	General Information
Bioanalytical method	Terlipressin and lysine-vasopressin concentrations in human plasma (K2EDTA) were determined by a validated high performance liquid chromatography coupled with tandem mass spectrometry assay using terlipressin-d_{13} and [Lys^8]-vasopressin-d_{11} as the respective internal standards.
Healthy subjects versus patients	The pharmacokinetics of terlipressin in patients with HRS-1 are similar to healthy adults.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Following a 1 mg Q6h IV bolus injection of Terlivaz, terlipressin median steady state C_{max} is 70.5 ng/mL (90% CI 37.1 to 142.9), median steady state AUC_{24h} is 123 ng×hr/mL (90% CI 61.2 to 246) and median steady state C_{ave} is 14.2 ng/mL (90% CI 8.34 to 22.9). Lysine-vasopressin median steady state C_{max} is 1.16 ng/mL (90% CI 0.40 to 3.36), median steady state AUC_{24h} is 11.2 ng×hr/mL (90% CI 3.78 to 33.5), and median steady state C_{ave} is 0.52 ng/mL (90% CI 0.19 to 1.49).
Dose proportionality	Plasma concentrations of terlipressin increase proportionately with dose after single IV injections of 5, 10, and 20 µg/kg in healthy adults.
Accumulation	Because of the short half-life and rapid clearance of terlipressin and lysine-vasopressin, the possibility of significant drug accumulation at steady state is small.
	Absorption
T_{max}	Terlipressin: ~at the end of the bolus injection Lysine-vasopressin: approximately 1 to 2 hours post-dose

Characteristic	Drug Information
	Distribution
Volume of distribution	Terlipressin: 6.3 L (23.3% CV); Lysine-vasopressin: 1370 L (18.8% CV)
Drug as substrate of transporters	Terlipressin is not a substrate of the human transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K.
	Elimination
Clearance	Terlipressin: 27.4 L/h (8.7%CV); Lysine-vasopressin: 318 L/h (11.5% CV)
Half-life	Terlipressin: 0.9 h; Lysine-vasopressin: 3 h
Metabolic pathway(s)	Terlipressin is degraded by several tissue peptidases in almost all organs. A greater degradation activity is reported in the liver and kidneys. The active metabolite, lysine-vasopressin, is formed by the stepwise cleavage of the terminal glycyl residues of terlipressin. Lysine-vasopressin undergoes rapid degradation via C-, N- terminus, and disulfide bond cleavage.
Primary excretion pathways (% dose)	<1% of the dose is elimination via kidney as terlipressin and lysine-vasopressin
	Intrinsic Factors and Specific Populations
Body weight	Clearance of terlipressin in patients with HRS-1 increases with body weight, whereas, body weight has no effect on the clearance or volume of distribution of lysine-vasopressin. No dose adjustment based on intrinsic factors is needed.
Age	Based on population PK analysis, no significant effect of age was observed on terlipressin exposure.
Renal impairment	No dose adjustment is required in patients with renal impairment.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Terlipressin is not a direct, time-dependent or metabolism-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes. Terlipressin does not induce CYP1A2, CYP2B6, and CYP3A4 enzymes.
Inhibition/induction of transporter systems	Terlipressin is not an inhibitor of the human transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K.

Source: NDA 22231-Summary of Clinical Pharmacology Studies, Study reports: RPT-STDY-0338, RPT-STDY-0339 and RPT - STDY -0340

Abbreviations: V1 receptor, vasopressin receptor 1; HRS-1, hepatorenal syndrome type 1; IV, intravenous; C_{max}, maximum observed plasma concentration; AUC_{24h}, area under the plasma concentration-time curve extrapolated to 24 hours; CI, confidence interval; C_{ave}, average concentration; T_{max}, time to maximum plasma concentration; CV, coefficient of variation; L/h, liters per hour; h, hour

5.1. Nonclinical Assessment of Potential Effectiveness

The submission does not contain new nonclinical data. According to the FDA Pharmacology-Toxicology Review dated August 6, 2009, the Applicant did not conduct any pharmacodynamic studies for the initial new drug application (NDA) submission.

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

The dosing regimen used in the CONFIRM study was the same as that used in Study OT-0401 and the REVERSE study. In OT-0401 and REVERSE, over 70% of subjects had no dose increase from the starting dose of 1 mg every 6 hours.

The starting dose of terlipressin in CONFIRM was 1 mg (one vial), administered as a bolus injection over 2 minutes. Doses were given every 6 hours (± 30 minutes). If, on Day 4 after a minimum of 10 doses of study drug, SCr had decreased, but by <30% from baseline, the dose was increased to 2 mg every 6 hours (± 30 minutes; 8 mg/day). The dose was not increased in subjects with coronary artery disease or in the setting of circulatory overload, pulmonary edema, or bronchospasm. If dosing was interrupted because of an adverse event, study drug could be restarted at the discretion of the investigator, at the same or lower dose. Study drug was not restarted if dosing was interrupted because of cardiac ischemia or mesenteric ischemia. After dose interruption, study drug could 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 could then be increased to the previous dose level.

In CONFIRM, study treatment was continued until 24 hours after two consecutive SCr values of not more than 1.5 mg/dL were obtained, or up to a maximum of 14 days (maximum of 15 days if SCr first reached 1.5 mg/dL on Day 14). If SCr was at or above the subject's baseline value on Day 4 (after a minimum of 10 doses), study treatment was discontinued. Study treatment was also discontinued if a subject was to undergo renal replacement therapy, liver transplantation, transjugular intrahepatic portosystemic shunt (TIPS) placement, was to receive vasopressor therapy, or experienced an adverse event of cardiac ischemia or mesenteric ischemia.

The proposed dosing regimen in labeling is in accordance with the dosing regimen used in the CONFIRM study. The incidence of HRS reversal by terlipressin dose level in the terlipressin-treated patients in the pooled intent-to-treat (ITT) population is supportive of the proposed dosing.

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Overview of Study

In support of the proposed indication and to address the 2009 complete response letter, the Applicant conducted a phase 3 study (MNK19013058) titled, "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)." The study was conducted from July 13, 2016, to July 24, 2019, at 60 sites: 55 sites in the United States and five sites in Canada.

6.2.2. Initial Protocol and Amendments

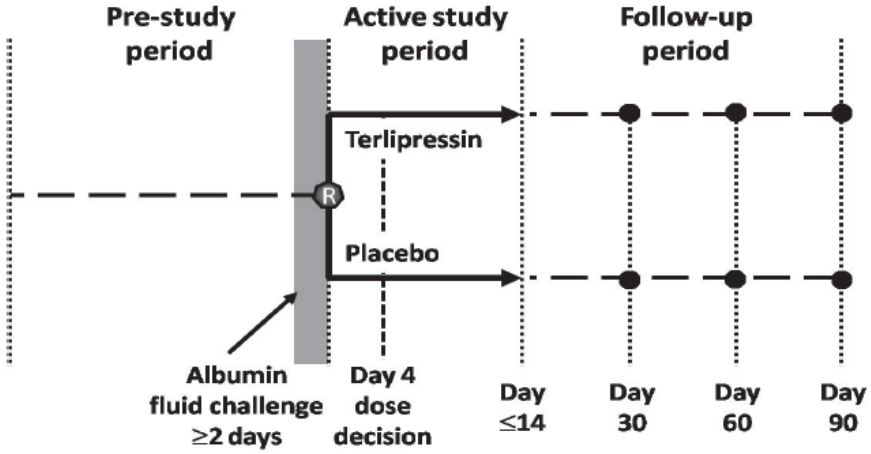
The original protocol was issued on March 1, 2016, and was amended three times (see Appendix III.15.2 for details regarding each amendment). The overview provided in this section is based on Amendment 1, dated May 9, 2016. This amendment incorporated revisions intended to address FDA recommendations in the SPA Agreement letter. Further amendments are noted where applicable.

6.2.3. Study Design

The CONFIRM study was a randomized, double-blind, placebo-controlled study comparing intravenous (IV) terlipressin to placebo. The study enrolled adults ≥18 years of age with HRS-1 (defined as rapidly progressive worsening in renal function to a SCr ≥2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks). Notable inclusions included no sustained improvement in renal function (<20% decrease in SCr and SCr ≥2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin.

Notable exclusions included SCr >7.0 mg/dL, clinical evidence suggesting parenchymal renal disease, severe cardiovascular disease, use of vasopressors (other than midodrine or octreotide) of ≥3 consecutive days within the prior 14-day screening period, TIPS within 30 days of randomization, and current or recent (within 4 weeks) RRT. The target enrollment was 300 subjects (randomized 2:1 to terlipressin versus placebo). An overview of the study design is shown in Figure 1.

Figure 1. CONFIRM Study Design



Source: Applicant, CONFIRM protocol

6.2.4. Study Objectives

The primary objective was to confirm the efficacy and safety of IV terlipressin versus placebo in the treatment of adult subjects with HRS-1 receiving standard of care albumin therapy.

6.2.5. Study Endpoints

Primary Endpoint

The primary endpoint was the incidence of verified HRS reversal, defined as two consecutive serum creatinine values ≤1.5 mg/dL at least 2 hours apart, while on treatment by Day 14, or discharge, whichever came first (on treatment defined as up to 24 hours after the final dose of study drug). Subjects needed to be alive without RRT for at least 10 days after achieving verified HRS reversal. Serum creatinine values after RRT, TIPS, liver transplant, or open-label vasopressor use were to be excluded from the primary endpoint analysis.

- RRT was defined as any procedure to replace nonendocrine kidney function and included intermittent hemodialysis, ultrafiltration, continuous hemofiltration and hemodialysis, peritoneal dialysis, and other dialysis and filtration techniques.
- SCr values obtained after midodrine administration were included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after August 17, 2018. SCr values obtained after the administration of a single dose of dobutamine were also included (Protocol Amendment 3, September 26, 2018; see Table 51 for further details on Amendment history)

Secondary Endpoints

The protocol specified four secondary endpoints with a plan to control the overall type 1 error rate, as described in Table 7.

Table 7. Secondary Endpoints

Secondary Endpoint	Details
Incidence of subjects with HRS-1 reversal	Percentage of subjects with a SCr value ≤1.5 mg/dL while on treatment by Day 14 or discharge. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use were excluded
Durability of HRS-1 reversal	Percentage of subjects with HRS reversal without RRT to Day 30
Incidence of HRS-1 reversal in SIRS subgroup	HRS-1 reversal was defined as percentage of subjects with a SCr value ≤1.5 mg/dL while on treatment by Day 14 or discharge The SIRS subgroup was identified based on meeting ≥2 of the following criteria: white blood cell count <4,000 or >12,000 cells/μL, heart rate >90 bpm, temperature >38ºC or <36ºC, respiratory rate >20/min, and bicarbonate level <21 mmol/L
Incidence of verified HRS-1 reversal without HRS-1 recurrence by Day 30	HRS-1 recurrence was defined as rapidly progressive worsening in renal function to SCr ≥2.25 mg/dL without sustained improvement in renal function at least 48 hours after diuretic withdrawal and beginning of plasma volume expansion with albumin

Source: Study Report pp.57-58
Abbreviations: HRS-1, hepatorenal syndrome type 1; SIRS, systemic inflammatory response syndrome; SCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic shunt; RRT, renal replacement therapy

6.2.6. Statistical Analysis Plan

The original statistical analysis plan (SAP) was issued on February 24, 2016. As discussed below, there were four SAP amendments.

Datasets

The SAP defined the following key datasets:

- **ITT analysis set:** All subjects randomly assigned to a treatment group according to randomized assignment regardless of actual treatment received.
- **Safety analysis set:** All randomized subjects who received at least one dose of study drug (terlipressin or placebo), classified on the basis of actual treatment received.

Efficacy Analyses

Primary and secondary efficacy analyses were based on the ITT dataset and included all positively adjudicated events that occurred between randomization and the global trial end date. The incidence of verified HRS reversal was defined as above. Serum creatinine values obtained after RRT, TIPS, liver transplant, or open-label vasopressor use were excluded from the primary endpoint analysis.

The four secondary endpoints were:

- Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value of no more than 1.5 mg/dL while receiving treatment by Day 14 or discharge (SCr values obtained after RRT, TIPS, liver transplant, or open-label vasopressor use were excluded)
- Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30
- Incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup, defined as the percentage of SIRS subjects with HRS reversal
- Incidence of verified HRS reversal without HRS recurrence by Day 30

Adjustment for Multiplicity

An O'Brien-Fleming boundary was used to adjust the alpha for the interim analysis and final analysis. The Hochberg multiple comparison procedure was used to control the familywise error rate for the four secondary endpoints. Because of the interim analysis, the targeted error rate used for the Hochberg procedure at the final analysis was adjusted to 0.048.

Subgroup Analyses

The subgroup of subjects with SIRS were analyzed as a secondary endpoint. This was the only planned subgroup analysis in the SAP.

Interim Analyses

One interim analysis was planned after approximately 50% of subjects had completed 14 days of follow-up in the study.

Sample Size Calculations

With a 2:1 randomization and assuming event rates of approximately 28% and 12.5%, a sample size of 300 subjects would provide approximately 90% power with a two-sided type 1 error rate of 0.05.

Baseline

For evaluations that are collected at multiple occasions prior to initiation of study drug, the latest non-missing evaluation prior to the start of study drugs was considered the “baseline” evaluation for analysis. In most cases, baseline was defined as Day 0 of the study period, but a pre-study period value was utilized if the Day 0 value was missing.

SAP Amendments

A summary of amendments to the SAP is shown in Table 8. The Applicant states that no unblinded data or analyses were available during conduct of the study or during the time of any protocol or SAP amendments.

Table 8. Overview of Statistical Analysis Plan Amendments

Amendment Number and Date	Summary of Changes
1. 5/10/2016	Sample size increased from 228 to 300 Definitions of primary and secondary endpoints described in more detail Multiple testing procedure for secondary endpoints changed from sequential testing to Hochberg procedure
2. 12/13/2016	Clarified definitions of secondary endpoints and HRS recurrence
3. 8/2/2017	Clarified only on treatment serum creatinine values would be allowed for definition of secondary endpoint HRS reversal
4. 9/27/2018	Clarified the scenarios where serum creatinine values for subjects using midodrine or dobutamine would be included to meet criteria for primary endpoint and secondary endpoints

6.3. Results of Analyses of Clinical Trials / Studies Intended to Demonstrate Benefit to Patients

6.3.1. Demographics

Baseline demographic characteristics were similar in the two treatment groups (see Table 9). The mean age was 54 years. Sixty percent of subjects were male. Overall, 90% of subjects were white, 6% were black or African American, and 2% were Asian. Sites in the United States accounted for 89% of subject enrollment.

Table 9. Baseline Demographic Characteristics, ITT Population, CONFIRM Study

Characteristic	Terlipressin (N=199)	Placebo (N=101)
Sex, n (%)		
Male	120 (60%)	59 (58%)
Age, years		
Mean (SD)	54.0 (11.3)	53.6 (11.8)
Median (min, max)	55 (23, 78)	55 (31, 82)
Race, n (%)		
White	177 (89%)	94 (93%)
Asian	5 (2%)	1 (1%)
Black/African American	12 (6%)	5 (5%)
Other/Unknown	5 (2%)	1 (1%)
Ethnicity, n (%)		
Hispanic	32 (16%)	13 (13%)
Non-Hispanic	165 (83%)	88 (87%)
Country of participation, n (%)		
United States	178 (89%)	89 (88%)
Canada	21 (11%)	12 (12%)

Source: Study Report Table 13; analysis confirmed by FDA reviewer
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; ITT, intent-to-treat

Baseline clinical characteristics were also well-balanced between treatment groups. Both groups had similar proportions of subjects with severe liver disease at baseline, as demonstrated by similar proportions of Child-Pugh Score Class C cirrhosis (indicative of decompensated cirrhosis) (62% terlipressin versus 60% placebo) and ACLF Grade 3 (indicative of ≥3 organ failures) (Arroyo and Jalan 2016) (20% terlipressin versus 18% placebo). Both groups also had similar proportions of subjects with alcoholic hepatitis at baseline.

Both arms had similar mean scores on measures that assessed risk of mortality over some time period, such as the Chronic Liver Failure-Sequential Organ Failure Assessment (an assessment used to predict 28-day mortality from chronic liver failure) (Arroyo and Jalan 2016) and the model for end-stage liver disease (MELD) (higher scores predict poorer 3-month survival). Other baseline liver disease characteristics, such as mean total bilirubin and proportion of subjects with alcoholic hepatitis, were similar between treatment arms.

Mean baseline SCr was similar in the two groups, 3.4 and 3.5 mg/dL in the terlipressin and placebo groups, respectively (subjects were stratified by qualifying SCr). Both treatment arms had similar vasopressor and diuretic use at baseline. Similar proportions of subjects had at least one large-volume paracentesis (≥4 L removed in one setting) prior to randomization (subjects were stratified by prior large volume paracentesis (LVP)). See Table 10 for details.

Table 10. Baseline Clinical Characteristics, ITT Population, CONFIRM Study

Characteristic (n (%))	Terlipressin (N=199)	Placebo (N=101)
Listed for liver transplant	56 (28)	20 (20)
Alcoholic hepatitis	81 (41)	39 (39)
MELD score	n=177	n=88
Mean (SD)	33 (6.6)	33 (6.2)
Median	34	34
Min, max	16, 40	17, 40
Total bilirubin (mg/dL)	n=188	n=99
Mean (SD)	12.5 (13.0)	15 (15.8)
Median	6.0	8.3
Min, max	0.3, 51.6	0.7, 98.0
ACLF grade		
0	0 (0)	0 (0)
1	99 (50)	41 (41)
2	60 (30)	42 (42)
3	40 (20)	18 (18)
CLIF-SOFA score	n=107	n=58
Mean (SD)	10.2 (2.4)	10.7 (2.4)
Median	10.0	11.0
Min, Max	5.0, 17.0	5.0, 18.0
Child-Pugh score		
Class A (score 5-6)	3 (1.5)	2 (2)
Class B (score 7-9)	68 (34)	32 (32)
Class C (score 10-15)	123 (62)	61 (60)
Missing	5 (2.5)	6 (6)
Qualifying serum creatinine, n (%)		
<3.4 mg/dL	111 (56)	55 (55)
≥3.4 mg/dL	88 (44)	46 (46)
Qualifying serum creatinine (mg/dL)		
Mean (SD)	3.4 (0.9)	3.5 (1.0)
Median (min, max)	3.2	3.2
Min, max	2.3, 6.6	2.3, 6.1
Any vasopressor use	145 (73)	77 (77)
≤1 day	44 (22)	20 (20)
>1 day and <3 days	28 (14)	17 (17)
≥3 days	73 (37)	40 (40)
Diuretic use prior to randomization	112 (56)	55 (55)
≥1 LVP[1] up to 14 days prior to randomization	76 (38)	42 (42)

Source: Study Report Tables 13, 14, 21, 14.1.3.1; ADSL and ADLB datasets
[1] LVP defined as ≥4 L removed in a single procedure
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; MELD, model for end-stage liver disease; ACLF, acute-on-chronic liver failure; CLIF-SOFA, Chronic Liver Failure–Sequential Organ Failure Assessment; LVP, large volume paracentesis; ITT, intent-to-treat

6.3.2. Disposition

Screening Period

A total of 344 subjects were screened. Of these, 20 failed to meet inclusion criteria and 15 met exclusion criteria. Nine subjects were eligible for randomization but were not randomized; four of those subjects were not randomized because they received a liver transplant.

Treatment Period

A total of 300 subjects were randomized: 199 to terlipressin and 101 to placebo. The disposition of subjects during the treatment period is shown in Table 11. All subjects who were randomized had complete data to ascertain whether or not they achieved verified HRS reversal. The Applicant confirmed RRT and vital status at 10 days for all patients who achieved verified HRS reversal.

Table 11. Study Disposition: Ascertainment of Primary Endpoint, ITT Population

N=300	Terlipressin n=199 (n (%))	Placebo n=101 (n (%))
Randomized	199	101
Treated	199 (100)	100 (99)
Subjects with data on verified HRS reversal	199 (100)	101 (100)
Subjects with verified HRS reversal[1]	n=58	n=16
Subjects with data on RRT and vital statuses 10 days post verified HRS reversal[2]	58 (100)	16 (100)

Source: FDA analysis
[1] Verified HRS reversal was defined as the percentage of subjects with two consecutive SCr values ≤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] Only those subjects who achieved verified HRS reversal were followed for RRT and vital status at Day 10. All subjects were followed for RRT and vital status at Days 30, 60, and 90
Abbreviations: HRS, hepatorenal syndrome; ITT, intent-to-treat; RRT, renal replacement therapy

Per the protocol, subjects were to be treated until one of the following occurred: verified HRS reversal, SCr at or above baseline value on study Day 4, initiation of RRT, liver transplant, TIPS procedure, or maximum duration of study drug received (i.e., 14 days). As shown in Table 12, approximately 73% of subjects discontinued treatment due to at least one of these protocol-specified dosing rules. A higher proportion of subjects in the placebo arm (36%) had SCr values at or above their baseline on Day 4 compared to the terlipressin arm (21%). A similar proportion of subjects in both arms discontinued treatment due to initiation of renal replacement therapy (7% terlipressin and 9% placebo). In the terlipressin arm, 10% of subjects discontinued treatment due to an adverse event, compared to 4% of subjects in the placebo arm.

Table 12. Study Disposition, Treatment Period, ITT Population

N=300	Terlipressin n=199 (n (%))	Placebo n=101 (n (%))
Randomized	199	101
Treated	199 (100)	100 (99)
Discontinued treatment per protocol[1]	148 (74)	71 (71)
Verified HRS reversal	72 (36)	17 (17)
SCr at or above baseline value on Day 4	42 (21)	36 (36)
Received maximum duration of study drug	11 (6)	6 (6)
Renal replacement therapy	13 (7)	9 (9)
Received liver transplant	9 (5)	3 (3)
Transjugular intrahepatic portosystemic shunt	1 (<1)	0 (0)
Discontinued treatment for other reasons[1]	51 (26)	30 (30)
Adverse event (not including death)	19 (10)	4 (4)
Death[2]	4 (2)	0 (0)
Physician decision	10 (5)	14 (14)
Request of subject or legal representative	7 (4)	5 (5)
Hospice/comfort/palliative care	7 (4)	2 (2)
Other	0 (0)	3 (3)
Withdrew consent	4 (2)	1 (1)
Other[3]	7 (4)	6 (6)

Source: Study Report Table 10; OCS Analysis Studio, Custom Table Builder
[1] Reason for study treatment discontinuation as reported by investigator on discontinuation form
[2] Review of narratives revealed that three of the four subjects continued to receive study treatment until death, whereas for one subject, treatment was discontinued 1 day prior to death due to declining clinical condition
[3] Other: discharged, randomized not dosed, no improvement in serum creatinine/other therapies initiated/withdrew from treatment
Abbreviations: ITT, intent-to-treat; HRS, hepatorenal syndrome; SCr, serum creatinine

Follow-Up Period

Approximately 10% of subjects in both treatment arms did not contribute follow-up data at Day 30, with the most common reason being “other” (i.e., subjects who could not be reached or attend follow-up visits, subjects who were in hospice, subjects who left hospital against medical advice, etc.).

As shown in Table 13, a large proportion of subjects died by the 30-day follow-up visit (38% on terlipressin and 35% on placebo), which is not unexpected given the patient population. The proportion of subjects who contributed to follow-up data at Day 90 (93% on terlipressin and 96% on placebo) was slightly greater than the proportion of subjects who contributed to follow-up data at Day 30 (91% on terlipressin and 90% on placebo).

Table 13. Study Disposition, Follow-up Period, ITT Population

Study Visit	Disposition (N=300)	Terlipressin n=199 (n (%))	Placebo n=101 (n (%))
30-day follow-up	Subjects who contributed to 30-day follow-up data	182 (91)	91 (90)
	Alive and completed study visit	108 (54)	56 (55)
	Death	74 (38)	35 (35)
	30-day SCr value known[2]	111 (56)	58 (57)
	Subjects who did not complete 30-day follow-up visit	17 (9)	10 (10)
	Lost to follow-up	0 (0)	3 (3)
	Consent Withdrawn	4 (2)	1 (1)
	Other[1]	13 (7)	6 (6)
60-day follow-up	Subjects who contributed to 60-day follow-up data	184 (92)	94 (93)
	Alive and contacted by telephone	93 (47)	53 (53)
	Death	91 (46)	41 (41)
	Subjects who did not contribute to 60-day follow-up data	15 (8)	7 (7)
	Lost to follow-up	0 (0)	3 (3)
	Consent Withdrawn	4 (2)	1 (1)
	Other[1]	11 (6)	3 (3)
90-day follow-up	Subjects who contributed to 90-day follow-up data	186 (93)	97 (96)
	Alive and contacted by telephone	85 (43)	52 (52)
	Death	101 (51)	45 (45)
	Subjects who did not contribute to 90-day follow-up data	13 (7)	4 (4)
	Lost to follow-up	1 (0.5)	0 (0)
	Consent Withdrawn	4 (2)	1 (1)
	Other[1]	8 (4)	3 (3)

Source: Study Report Figure 3; verified by FDA reviewer, ADLB, DS datasets
N.B.: Category of "Other" is not cumulative; categories of lost to follow-up, consent withdrawn, and death are cumulative
[1] Other: subjects who could not be reached or attend follow-up visits, subjects who were in hospice, subjects who left hospital against medical advice
[2] Number of subjects with data on SCr values at Day 30 exceeded the number of subjects who were alive and completed the Day 30 follow-up visit because a visiting phlebotomist drew SCr blood samples for subjects who were unable to attend the 30-day follow-up visit in person (three subjects on terlipressin and two subjects on placebo)
Abbreviations: SCr, serum creatinine; ITT, intent-to-treat

Protocol Deviations

A total of 17 terlipressin subjects (9%) and four placebo subjects (4%) had one or more protocol deviations that were considered "important" by the Applicant (see Table 14). One subject was randomized to placebo but incorrectly received a terlipressin dose on Day 2. One subject was randomized to placebo and did not receive treatment. The reason for not receiving treatment was listed as "not meeting inclusion/exclusion criteria." Both subjects continued to be followed and were included in the ITT analysis set.

The most common deviation was "Concomitant vasopressor in 2 consecutive days while receiving study drug" for the terlipressin arm (eight subjects [4%]). Although a higher proportion of subjects had "important" protocol deviations in the terlipressin arm compared to the placebo arm, the overall number of subjects with "important" protocol deviations was small for both treatment arms.

On May 30, 2018, the study statistician was accidentally unblinded to the treatment assignment for subject (b) (6) in an email communication from a Data Safety Monitoring Board (DSMB) member received through the vendor who oversaw the DSMB. After this occurred, the DSMB charter was revised to clarify how data and the communication process between the DSMB, vendor, and Applicant were to be handled. No other study team members were unblinded.

Neither this event of unblinding nor the protocol violations raise concern about the integrity of the study or interpretability of the data.

Table 14. Important Protocol Deviations, ITT Population

N=300	Terlipressin n=199 (n (%))	Placebo n=101 (n (%))
Subjects with important protocol deviations	17 (9)	4 (4.0)
Concomitant vasopressor in 2 consecutive days while receiving study drug	8 (4)	1 (1)
Inclusion/exclusion violation	1 (0.5)	1 (1)
Randomized, not dosed	0 (0)	1 (1)
Received study drug after a stop order from physician	1 (0.5)	0 (0)
Received study drug from an incorrect kit	0 (0)	1 (1)
RRT while receiving study drug	4 (2)	1 (1)
Starting dose of 0.5 mg/dL	2 (1)	0 (0)
Time between doses <3 hours	3 (2)	0 (0)

Source: Study Report Table 11; verified by FDA reviewer
Abbreviations: ITT, intent-to-treat, RRT, renal replacement therapy

6.3.3. Analysis of Primary Endpoint

The primary endpoint was the incidence of verified HRS reversal, which was defined as the percentage of subjects with two consecutive SCr values ≤1.5 mg/dL at least 2 hours apart while on treatment by Day 14, or discharge (on treatment was defined as up to 24 hours after the final dose of study drug). In addition, subjects had to be alive without RRT for at least 10 days after achieving verified HRS reversal. As shown in the table below, the study met its primary endpoint. See Appendix III.16 for details regarding the calculation of the primary endpoint.

Table 15. Primary Endpoint, Verified HRS Reversal, ITT Population

	Terlipressin (N=199)	Control (N=101)
Verified HRS reversal[1], n (%)	58 (29%)	16 (16%)
Z score	2.53	
P-value	0.012	

Source: Study Report Table 27; Analysis confirmed by FDA statistical reviewer
[1] Defined as two consecutive serum creatinine (SCr) values ≤1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge (on treatment was defined as up to 24 hours after the final dose of study drug). Subjects had to be alive without renal replacement therapy (RRT) for at least 10 days after achieving verified HRS reversal. SCr values after RRT, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressor use were excluded from the primary end point analysis
Abbreviations: HRS, hepatorenal syndrome; ITT, intent-to-treat

Analysis to Address Durability of Treatment Effect

Analyses were conducted to determine the durability of the treatment effect on the primary endpoint, verified HRS reversal. The clinical protocol prespecified criteria for determination of HRS recurrence by the investigator (see Appendix III.15.5 of this document for details). Review of the clinical protocol and study report revealed that HRS recurrence was adequately captured during the study. Of the 58 subjects on terlipressin who met the primary endpoint of verified HRS reversal, 10 subjects (17%) met the prespecified criteria for HRS recurrence by Day 30, and HRS recurrence could not be excluded for three subjects (5%). Hence, the proportion of subjects with HRS recurrence may have been as high as 22% in the terlipressin group. None of the 16

placebo arm subjects who met the primary endpoint of verified HRS reversal met criteria for HRS recurrence by Day 30 (see table below).

Table 16. HRS Recurrence in Subjects With Verified HRS Reversal

n (%)	Terlipressin N=58	Placebo N=16
Met criteria for HRS recurrence by Day 30[1]	10 (17)	0 (0)
Could not exclude HRS recurrence	3 (5)	0 (0)

Source: FDA analysis
[1] HRS recurrence defined as: 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 and without sustained improvement in renal function (<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 a bumin
Abbreviations: HRS, hepatorenal syndrome; SCr, serum creatinine

See Appendix III.16 for an analysis of the durability of HRS reversal in the subgroup of subjects who did not receive a liver transplant.

Sensitivity Analyses

The applicant conducted two sensitivity analyses on the primary endpoint. For the first analysis, which was prespecified in the SAP, the requirement that subjects be alive without RRT for at least 10 days after achieving verified HRS reversal was removed. The second sensitivity analysis, which was not pre-specified, excluded SCr values obtained after midodrine administration if midodrine was started on Day 1 and was administered for no more than 24 hours and if the subject was enrolled on or after August 17, 2018, and those obtained after a single-dose of dobutamine (see Table 51 for further details). As shown in Table 17, the results of these analyses were consistent with the main analysis.

Table 17. Primary Endpoint Sensitivity Analyses, ITT Population

Sensitivity Analysis	Terlipressin (N=199)	Control (N=101)	Z Score	P-Value
Verified HRS reversal without Day 10 exclusions[1], n (%)	69 (35%)	18 (18%)	3.04	0.002
Verified HRS reversal with vasopressor criteria removed,[2] n (%)	60 (30%)	16 (16%)	2.69	0.007

Source: Study Report Tables 14.2.1.2.1 and 14.2.1.2.2
[1] Day 10 exclusions: subjects had to be alive without RRT for at least 10 days after achieving verified HRS reversal
[2] Vasopressor criteria: (1) SCr values obtained after midodrine administration be included if midodrine was started on Day 1 and was administered for no more than 24 hours and if the subject was enrolled on or after August 17, 2018, and (2) including SCr values obtained after a single dose administration of dobutamine
Abbreviations: HRS, hepatorenal syndrome; ITT, intent-to-treat; SCr, serum creatinine

As seen in the table below, treatment effects on renal function (SCr) as a continuous variable were consistent with the primary endpoint finding. At the end of treatment, subjects in the terlipressin group had a lower mean SCr (2.8 (SD 1.7) mg/dL) compared to subjects in the placebo group (3.7 (SD 1.8) mg/dL).

Table 18: **Summary of Serum Creatinine in CONFIRM, ITT**

Serum Creatinine (mg/dL)	Terlipressin N=199	Placebo N=101
Qualifying SCr		
Mean (SD)	3.4 (0.9)	3.5 (1.0)
Median (min, max)	3.2 (2.3, 6.6)	3.2 (2.3, 6.1)
End of Treatment		
Mean (SD)	2.8 (1.7)	3.7 (1.8)
Median (min, max)	2.3 (0.8, 8.5)	3.4 (1.0, 8.1)

Reviewer Analysis, adlb and adeff datasets
Abbreviations: SCr, serum creatinine; min, minimum; max, maximum

Subgroup Analyses

As seen in the table below, exploratory subgroup analyses of the primary endpoint based on age and sex were consistent with the overall efficacy findings. The vast majority of subjects in the study were white (90%), limiting the ability to conduct or interpret subgroup analyses in subjects who were not.

Additional subgroup analyses are described in detail below.

Table 19. Verified HRS Reversal Within Subgroups, ITT Population

Characteristic	Terlipressin n/N (%)	Placebo n/N (%)
All Subjects	58/199 (29%)	16/101 (16%)
Sex, n (%)		
Male	35/120 (29%)	9/59 (15%)
Female	23/79 (29%)	7/42 (17%)
Age, years		
<65	47/164 (29%)	14/83 (17%)
≥65	11/35 (31%)	2/18 (11%)
Race, n (%)		
White	53/177 (30%)	14/94 (15%)
Non-White/Unknown	4/22 (18%)	2/7 (29%)
Country, n (%)		
United States	48/178 (27%)	14/89 (16%)
Canada	10/21 (48%)	2/12 (17%)

Source: Study Report Table 53; verified by FDA reviewer
Abbreviations: N, number of subjects in treatment group; n, number of subjects with verified hepatorenal syndrome reversal

Subgroup analysis in patients with and without alcoholic hepatitis at baseline

During the Cardiovascular and Renal Drugs Advisory Committee meeting on July 15, 2020, one of the Advisory Committee members opined that the data supported efficacy in patients with alcoholic hepatitis at baseline, but questioned whether terlipressin provided benefit in patients without alcoholic hepatitis at baseline. As shown in the table below, the point estimate of the treatment effect on HRS reversal was numerically greater in the subgroup categorized as having alcoholic hepatitis at baseline compared to those without. The results of exploratory analyses of outcomes, such as RRT-free survival, in patients with and without alcoholic hepatitis were largely consistent with the findings for HRS reversal (see Appendix section III.16).

The Division of Hepatology and Nutrition (DHN) was asked to opine on whether there might be a biologic basis for such a finding. DHN noted the challenges of interpreting subgroup analyses, but also indicated there could be a biologic basis for the finding. According to the DHN,

proinflammatory mechanisms play a significant role in the pathogenesis of alcoholic hepatitis, similar to the pathogenetic mechanisms in SIRS (see analyses of SIRS subgroups below). Alcoholic hepatitis sets off a series of pro-inflammatory cytokines that lead to additional vasodilatation of the peripheral vasculature and eventual reduction in renal perfusion pressure. DHN hypothesized that terlipressin may have exerted an anti-inflammatory effect, in addition to its vasoconstrictive effect, that further reduced portal venous pressure and in turn, improved renal perfusion pressure, thus improving renal function to a greater extent in patients with alcoholic hepatitis compared to those without.

Table 20. Verified HRS Reversal Within Alcoholic Hepatitis Subgroups, ITT Population

Verified HRS Reversal	Terlipressin n/N (%)	Placebo n/N (%)	Risk Difference (%) (95% CI)	P-Value
Alcoholic hepatitis present at baseline	25/81 (31%)	3/39 (8%)	23% (7.0, 39.3)	0.005
Alcoholic hepatitis not present at baseline	33/118 (28%)	13/62 (21%)	7% (-6.4, 20.4)	0.31

Source: FDA analysis
Abbreviations: HRS, hepatorenal syndrome; N, number of subjects in treatment group; n, number of subjects with verified HRS reversal; CI, confidence interval; ITT, intent-to-treat

Subgroup analysis in patients with and without SIRS at baseline

Patients with decompensated liver disease frequently have SIRS criteria in the absence of uncontrolled infection or sepsis due to presence of proinflammatory mechanisms as a result of their underlying disease. The extent of overlap between the subgroups with SIRS and alcoholic hepatitis in the study is unclear. As shown in the table below, the point estimate of the treatment effect on HRS reversal was numerically greater in the subgroup categorized as having SIRS at baseline compared to those without. While there may be a biologic basis for this finding, it is unclear, at this time, whether this difference is real.

Table 21. Verified HRS Reversal Within SIRS Subgroups, ITT Population

Verified HRS Reversal	Terlipressin n/N (%)	Placebo n/N (%)
SIRS present at baseline	22/84 (26%)	2/48 (4%)
SIRS not present at baseline	36/115 (31%)	14/53 (26%)

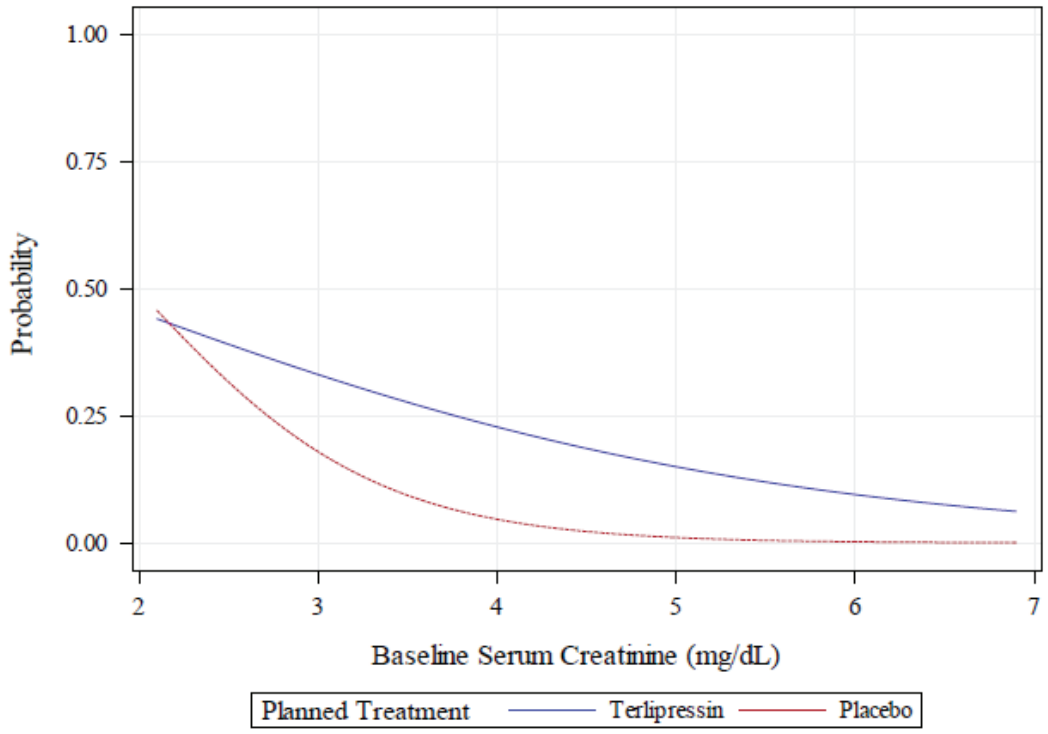
Source: Applicant
Abbreviations: HRS, hepatorenal syndrome; N, number of subjects in treatment group; n, number of subjects with verified HRS reversal; CI, confidence interval; ITT, intent-to-treat; SIRS, systemic inflammatory response syndrome

Subgroup analyses by baseline serum creatinine

It is believed that implementing interventions at earlier stages of HRS could result in greater efficacy. The figure below shows the probability of achieving HRS reversal in the two treatment arms by baseline serum creatinine level. The analysis indicates that the probability of achieving verified HRS reversal decreases, regardless of treatment arm, as baseline SCr increases and suggests that the magnitude of the benefit (as assessed by terlipressin's effect on HRS reversal) decreases with increasing baseline SCr.

The Applicant asserts that the findings from these analyses align with their risk mitigation proposal, which excludes patients with SCr ≥5 mg/dL, a subgroup less likely to benefit from terlipressin (see section 7.7.1 for details).

Figure 2: Predicted Probability of Verified HRS Reversal Based on Baseline Serum Creatinine, ITT



Source: Applicant, reviewed by FDA

6.3.4. Analysis of Secondary Endpoints

The SAP specified four secondary endpoints that were to be tested using the Hochberg procedure to control the overall type 1 error rate. Like the primary endpoint, these endpoints assessed treatment effects on HRS reversal, such as the durability of the response.

Because the primary endpoint analysis was successful, the secondary endpoints were tested at an alpha level of 0.048 for a Z score of 1.98. As shown in Table 22, compared to subjects in the placebo arm, more subjects in the terlipressin arm experienced HRS reversal[3] while on treatment by Day 14 or discharge ($p<0.001$) and HRS reversal without RRT to Day 30 ($p=0.003$).

The incidence of HRS reversal while on treatment by Day 14 or discharge in the SIRS subgroup was also greater in the terlipressin arm as compared to the placebo arm ($p<0.001$). The proportion of subjects with verified HRS reversal without HRS recurrence by Day 30 was numerically greater in the terlipressin arm, but the difference between groups was not statistically significant (24% terlipressin versus 16% placebo, $p=0.09$).

The SAP also prespecified a sensitivity analysis on the secondary endpoint of incidence of verified HRS reversal without HRS recurrence by Day 30 in which all subjects where the investigator could not exclude a recurrence of HRS-1 were treated as having a recurrence (three

[3] Defined as one SCr value ≤1.5 mg/dL. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor were excluded

subjects on terlipressin, zero subjects on placebo). The results were consistent with the results of the corresponding secondary endpoint (45/199 (23%) terlipressin versus 16/101 (16%) placebo, p=0.163).

Table 22. Secondary Endpoint, ITT Population[1]

N=300	Terlipressin n=199 (n (%))	Placebo n=101 (n (%))	P-Value
Incidence of patients with HRS reversal[2] while on treatment[3] by Day 14 or discharge	72 (36)	17 (17)	<0.001
Percentage of subjects with HRS reversal without RRT to Day 30 ("Durability of HRS reversal")	63 (32)	16 (16)	0.003
Incidence of HRS reversal in the SIRS subgroup while on treatment[3] by Day 14 or discharge	N=84 28 (33)	N=48 3 (6)	<0.001
Incidence of verified HRS reversal without HRS recurrence by Day 30	48 (24)	16 (16)	0.092

Source: Study Report Tables 28, 29, 30, 31
[1] See Table 7 in this document for detailed definitions of each secondary endpoint
[2] HRS reversal defined as one SCr value ≤1.5 mg/dL. Serum creatinine values after RRT, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressor were excluded
[3] On-treatment defined as up to 24 hours after the final dose of study drug
Abbreviations: HRS, hepatorenal syndrome; RRT, renal replacement therapy

6.3.5. Exploratory Analyses

Treatment Effects on Receiving a Liver Transplant

The outcome of patients with HRS-1, including the recovery of renal function, is highly dependent on the reversal of hepatic failure (Cassinello et al. 2003). In patients with irreversible liver disease (i.e., advanced cirrhosis), liver transplant is the only definitive treatment for HRS-1 and has been associated with improved survival and long-term renal function in patients with HRS (Utako et al. 2018).

Post hoc analyses were conducted to assess the incidence of liver transplant in the terlipressin and placebo arms in the CONFIRM study. As seen in Table 23, a slightly higher proportion of subjects in the terlipressin arm were listed for liver transplant at baseline compared to the placebo arm (28% versus 20%, respectively). However, by the end of the study, the proportions of subjects who were listed for liver transplant at any time were similar in both arms (37% for terlipressin versus 35% for placebo). By Day 90, a lower proportion of subjects listed for a liver transplant at any time in the terlipressin arm compared to the placebo arm had received a liver transplant (62% versus 83%, respectively). Twenty-five percent of subjects on terlipressin who were listed for a transplant at baseline did not receive a liver transplant by Day 90 and died, compared to none in the placebo arm. The Kaplan-Meier (K-M) curves of treatment effect on time to liver transplant show a slight early separation between treatment arms (see Figure 3).

The CONFIRM study was not designed to systematically collect data on the reasons why some subjects who were listed for transplant were later suspended or removed from the transplant wait list. The Applicant speculated three possible factors for the decreased proportion of liver transplants in the terlipressin arm, which were: (1) an improvement in MELD score resulting in a

lower prioritization on the transplant list for some subjects,[4] (2) terlipressin causing an adverse event that delayed or prevented transplantation, and/or (3) factors independent of treatment that were not part of the randomization process but that influenced transplantation (e.g., blood type, geographic region, baseline MELD score, available support systems). We agree that it is challenging to interpret these analyses and that it may not be realistic to expect that treating HRS will translate into a higher incidence of liver transplantation given the scarcity of organs and current prioritization algorithm.

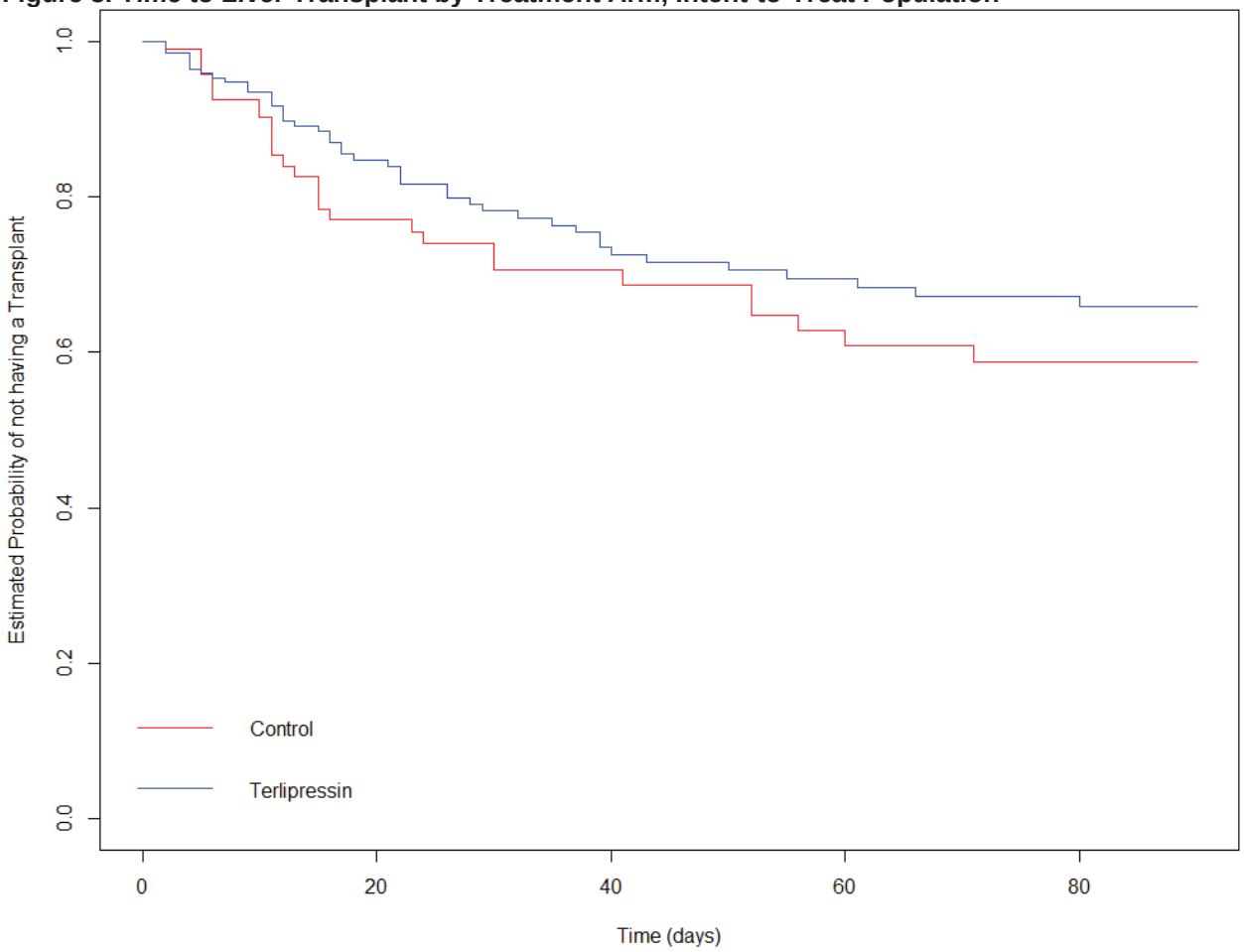
Table 23. Summary of Liver Transplant by Day 90, by Treatment Arm, ITT Population

N=300	Terlipressin (n/N (%))	Placebo (n/N (%))
Listed for transplant at baseline	56/199 (28)	20/101 (20)
Did not receive a liver transplant by Day 90	22/56 (39)	4/20 (20)
Died by Day 90	14/56 (25)	0/20 (0)
Alive by Day 90	8/56 (14)	4/20 (20)
Received a liver transplant by Day 90	34/56 (64)	16/20 (80)
Died by Day 90	0/56 (0)	1/20 (5)
Alive by Day 90	34/56 (64)	15/20 (75)
Listed for liver transplant at any time	74/199 (37)	35/101 (35)
Received a liver transplant by end of treatment	12/74 (16)	3/35 (9)
Received a liver transplant through Day 90	46/74 (62)	29/35 (83)

Source: Study Report, Table 14.3.4.17; verified by FDA reviewer, adsl dataset and confirmsubjectstatus30aug2019.xlsx
Abbreviation: ITT, intent-to-treat

[4] Patients awaiting liver transplantation are ranked according to their MELD score, a scoring system for assessing the severity of chronic liver disease, with higher scores indicating more severe disease. The MELD score uses the values for serum bilirubin, SCr, and the international normalized ratio for prothrombin time in its calculation. Paradoxically, an improvement in SCr through HRS reversal would decrease a patient's MELD score, and therefore, could increase the time to liver transplant (i.e., move a patient further down the transplant list).

Figure 3. Time to Liver Transplant by Treatment Arm, Intent-to-Treat Population



Source: FDA analysis

6.4. Review Issues Relevant to the Evaluation of Benefit

6.4.1. Effects on Clinical Outcomes Thought To Be Predicted by HRS Reversal

Issue

Although FDA agreed to the primary endpoint used in CONFIRM, during discussions of the trial, FDA also emphasized that the primary endpoint captured treatment effects on a laboratory parameter (serum creatinine), and as such, FDA considered the endpoint to be a surrogate endpoint. While FDA acknowledged the challenges associated with designing trials to detect effects on clinical outcomes associated with HRS-1, FDA also stated that should the trial succeed on the primary endpoint, FDA would expect favorable trends in clinical outcomes thought to be predicted by successfully treating HRS-1. Hence, both FDA and the applicant conducted the following analyses to assess treatment effects on clinical outcomes associated with HRS and/or

thought to be predicted by treatment effects on kidney function: RRT initiation and/or survival, outcomes post-liver transplant, and length of intensive care unit (ICU) stay.

Assessment

RRT-Free Survival

Overall Population

HRS-1 is associated with high mortality. Patients with HRS-1 who do not respond to medical interventions may also require RRT.

Post hoc analyses were conducted to assess the impact of terlipressin on these clinical outcomes in the CONFIRM study. Per the Applicant, systematic data on RRT characteristics were only collected during the 14-day treatment period. After the treatment period, only the frequency and number of times a subject received RRT from the previous assessment was recorded.

As discussed elsewhere in this review, treatment with terlipressin was not associated with improved survival in the CONFIRM study (in fact, the proportion of subjects who died was numerically greater in the terlipressin as compared to the placebo arm). Treatment effects on RRT-free survival are shown in Table 24 and the K-M curves in Figure 4 and Figure 5.

As shown in Table 24, RRT-free survival was slightly greater in the terlipressin as compared to the placebo arm, reflecting lower use of RRT in subjects randomized to terlipressin.

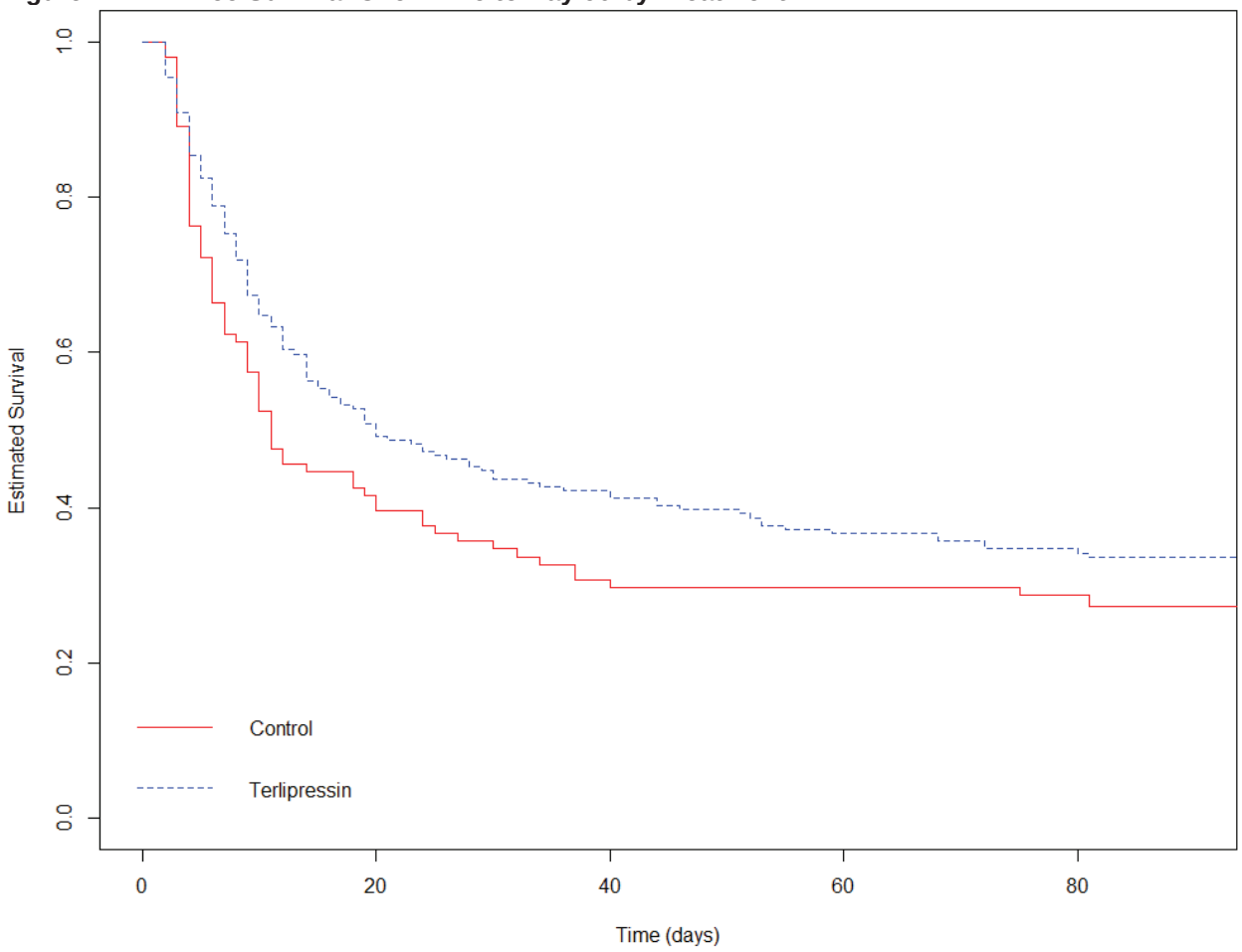
The K-M curves in Figure 5 isolate treatment effects on RRT from those on survival to Day 90. The K-M curves for RRT separate early in the trial, favoring the terlipressin arm. The K-M curves for survival cross several times then separate slightly (Day 40).

Table 24. Summary of Initiation of RRT and/or Death to Day 90, by Treatment Arm, ITT Population

Event	Terlipressin (N=199)	Control (N=101)	P-Value
RRT-free survival	67 (34%)	28 (28%)	0.09[1]
RRT initiation or death	132 (66%)	73 (72%)	0.09[1]
RRT initiation	58 (29%)	39 (39%)	0.07[2]
Death without preceding RRT	74 (37%)	34 (34%)	0.64[2]
Death with or without preceding RRT[3,4]	103 (52%)	47 (47%)	0.5[2]

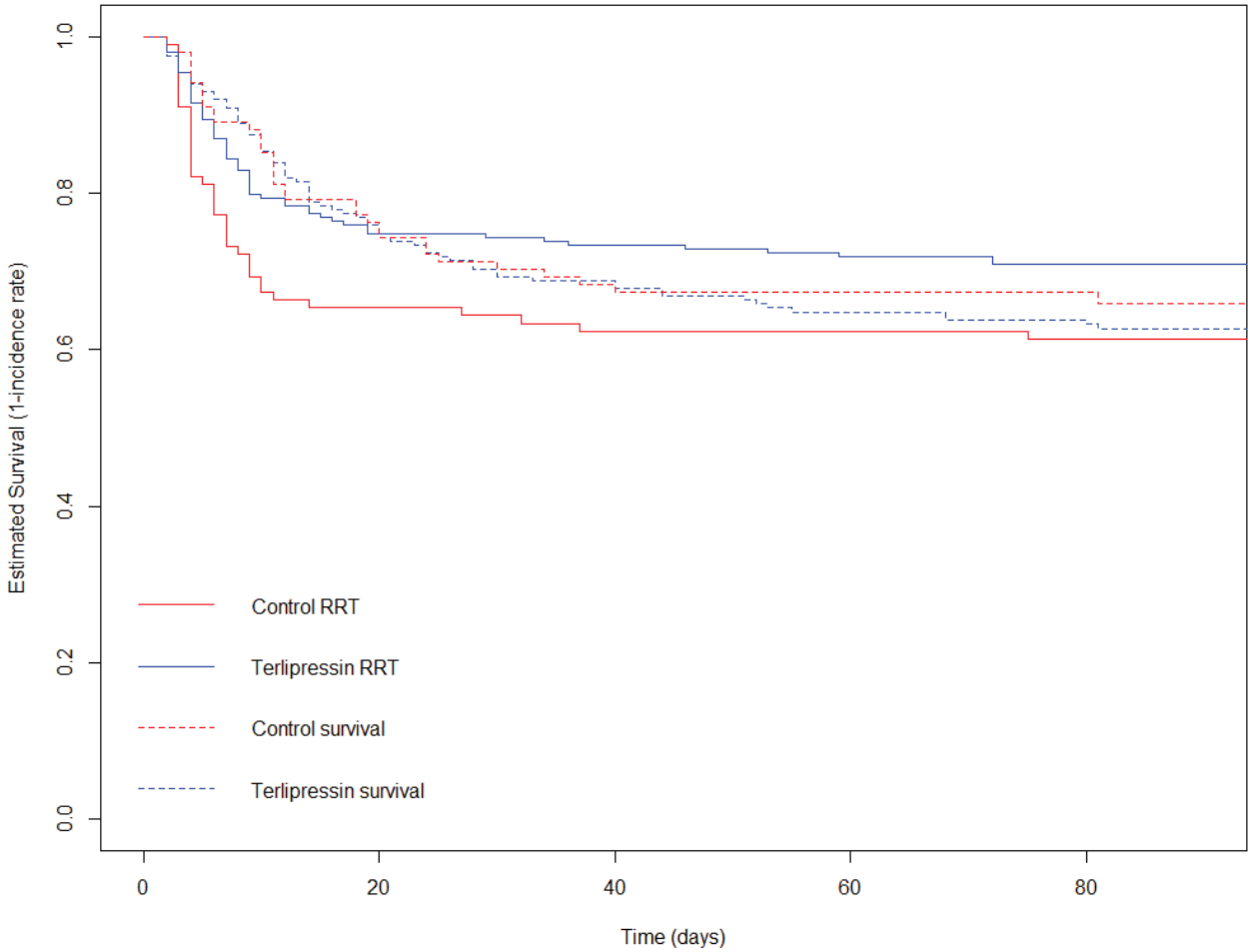
Source: FDA analysis, dataset tte1
[1] P-value from log rank test
[2] (Gray 1988)
[3] An information request was sent to the Applicant related to discrepancies in the number of deaths by treatment arm in different datasets/tables. Per the Applicant, the tte1 dataset includes deaths after database lock, which were not included in the adae dataset
[4] One subject on placebo who died by Day 90 did not receive study treatment, but was included in the ITT analysis
Abbreviations: ITT, intent-to-treat; RRT, renal replacement therapy

Figure 4. RRT-Free Survival Over Time to Day 90 by Treatment Arm



Source: FDA analysis
Abbreviation: RRT, renal replacement therapy

Figure 5. Competing Risks for RRT-Free Survival Over Time to Day 90 by Treatment Arm[1]



Source: FDA analysis
[1]The K-M curves isolate treatment effects on RRT to Day 90 from those on survival
Abbreviation: RRT, renal replacement therapy

See Appendix III.16 for analyses of RRT-free survival in the subgroup of patients who did not receive a liver transplant.

Outcomes Post-Liver Transplant

Post-Transplant RRT-Free Survival

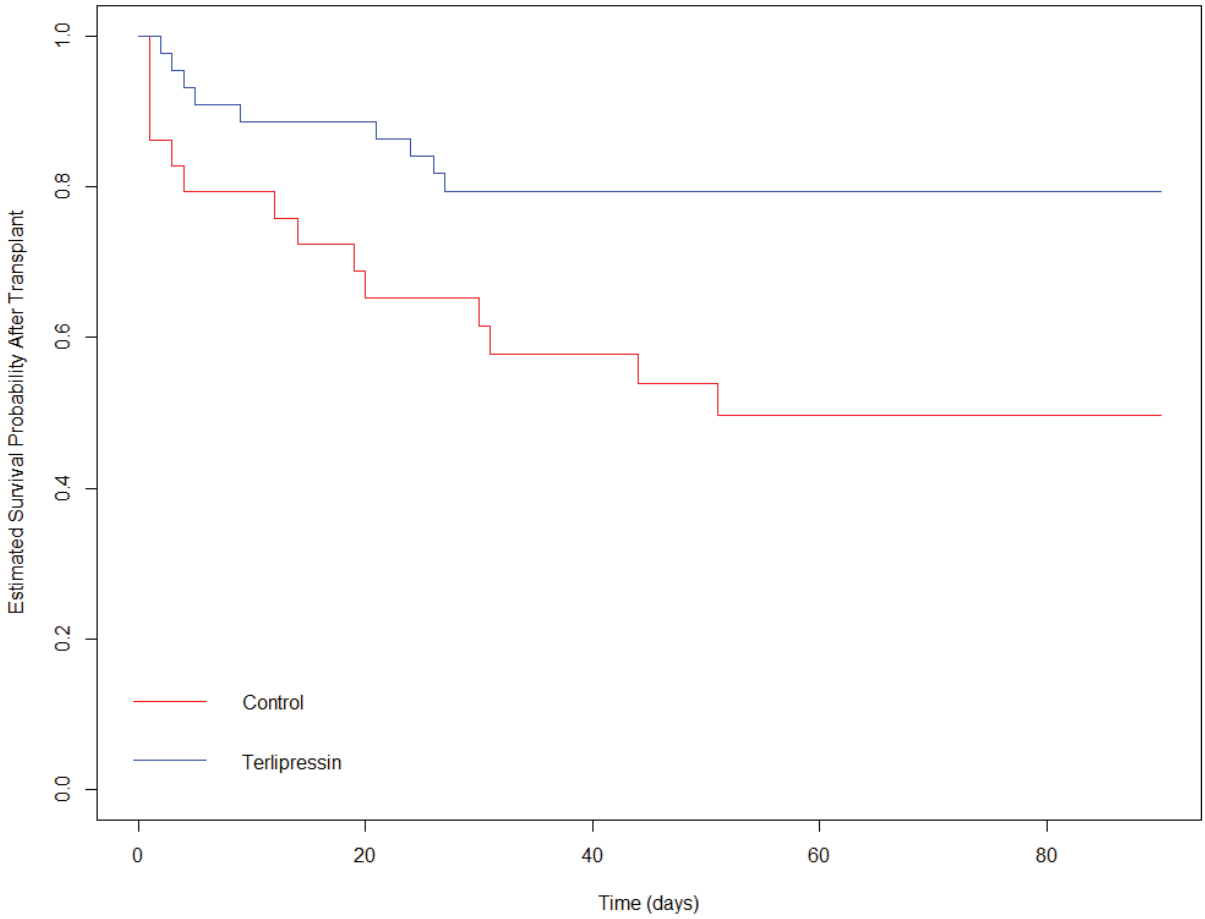
Improving renal function by reversing HRS prior to liver transplant has been associated with improved post-transplant outcomes (i.e., improved survival and renal function post-transplant). Post hoc analyses were conducted to determine the proportion of subjects in each arm who died or initiated RRT between transplant and Day 90. All subjects who received a liver transplant were included in the analysis, regardless of RRT-status pre-transplant (see Appendix III.16 for details on RRT-status before and after liver transplant). The results of these analyses are shown in Table 25 and K-M curves are shown in Figure 6). The proportion of subjects who initiated RRT after receiving a liver transplant was lower in the terlipressin arm than in the placebo arm. Interpretation of these analyses is difficult, because they are based on post-randomization variables.

Table 25. Summary of Initiation of RRT and/or Death to Day 90 by Treatment Arm in Subjects Who Received Liver Transplant, ITT Population

Event	Terlipressin (N=46)	Control (N=29)
RRT initiation or death	9 (20%)	14 (48%)
RRT initiation	9 (20%)	13 (45%)
Death without preceding RRT	0 (0%)	1 (3%)
Death with or without preceding RRT	0 (0%)	2 (7%)

Source: FDA analysis, dataset tte1
Abbreviations: RRT, renal replacement therapy; ITT, intent-to-treat

Figure 6. RRT-Free Survival Over Time to Day 90 by Treatment Arm for Subjects Who Received a Liver Transplant, ITT Population



Source: FDA analysis
Abbreviations: RRT, renal replacement therapy; ITT, intent-to-treat

Intensive Care Unit Length of Stay

The Applicant conducted analyses on the differences in ICU length of stay between treatment arms, a clinical outcome thought to be predicted by successfully treating HRS-1. Per the Applicant's analyses, a similar proportion of patients were admitted to the ICU in both groups; however, patients in the terlipressin as compared to the placebo group had shorter average lengths of ICU stay. Information is not provided on the disposition of patients following their

ICU stay (e.g., transfer to hospice, in-hospital transfer, transfer to home or a different hospital). There was also no difference in length of overall hospitalization between the two arms. See Table 26 for details.

The mortality data for patients who were transferred to the ICU do not suggest a benefit. Based on the information provided by the Applicant, it appears that 81% of patients admitted to the ICU in the terlipressin arm died over the observation period as compared to 64% in the placebo arm (see Table 26).

The Applicant also conducted a sensitivity analysis where lengths of ICU stay were calculated for the terlipressin and placebo groups after removing patients from the analysis who died during their ICU stay (data not shown). The results were consistent with the initial analysis (mean (SD) 5.8 (3.9) days versus 17.9 (20.0) days, respectively; median (min, max) 4.0 (2.0, 14.0) days versus 10.5 (3.0, 59.0) days, respectively).

Table 26. Summary of Patients Transferred to Intensive Care Unit During Initial Hospitalization, ITT

	Terlipressin N=199	Control N=101
Patients transferred to ICU	31 (16%)	14 (14%)
Deaths (n/N (%))	25/31 (81%)	9/14 (64%)
Average length of ICU stay (days)		
Mean (SD)	6.4 (5.5)	13.2 (15.9)
Median (min, max)	4 (1, 28)	8 (2, 59)
Average length of overall hospitalization (days)		
Mean (SD)	24.5 (19.0)	24.8 (18.3)
Median (min, max)	19 (4, 172)	21 (4, 117)

Source: Applicant
Abbreviations: ICU, intensive care unit; ITT, intent-to-treat

Conclusion

Exploratory analyses on clinical outcomes thought to be predicted by successfully treating HRS-1 suggest a trend in improvement for RRT-free survival in the terlipressin arm, but do not suggest a mortality benefit. Treatment effects on post-transplant RRT-free survival and ICU length of stay are challenging to interpret.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The clinical signs and toxicity noted in toxicology studies were generally consistent with pharmacologic effects of terlipressin and correlated with dose. See the FDA Pharmacology-Toxicology Review dated August 6, 2009, for further detail.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Terlipressin is a vasopressin analog. Key known and potential serious risks based on terlipressin's effects on V_1 receptors include: ischemic complications, gastrointestinal (GI) symptoms and disorders, respiratory effects, and bradycardia (terlipressin increases mean arterial pressure [MAP] and decreases heart rate [HR]). Potential key risks based on effects on V_2 receptors include hyponatremia and fluid retention.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Terlipressin is not currently approved for marketing in the U.S. but is available in over 40 countries outside the U.S., where it is the current standard of care in patients with decompensated cirrhosis complicated with HRS-1 (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018). The Division of Pharmacovigilance I analyzed postmarket safety data from case reports or case series for terlipressin from the FDA Adverse Event Reporting System database, VigiBase, and medical literature and identified the following three groups of postmarket adverse events (AEs) of concern reported with the use of terlipressin: 1) ischemia/necrosis, 2) cardiac adverse events (including arrhythmias), and 3) hyponatremia.

The ischemia/necrosis related events identified in postmarketing cases were generally consistent with events observed in the terlipressin clinical studies. However, postmarketing cases were more severe and were accompanied with serious outcomes, including death, and manifested in several forms at various locations of the skin, gastrointestinal tract, muscles (cardiac and non-cardiac), and the extremities. Serious extremity manifestations included reports of gangrene and osteomyelitis/osteonecrosis leading to amputations and extensive epidermal necrosis leading to diffuse desquamation. No cases of skin necrosis directly attributable to ischemic AEs were reported in the clinical studies, see Sections 7.6.2 and 7.6.5.1.

The cardiac AEs identified in postmarketing cases were also generally consistent with events observed in clinical studies. However, additional adverse cardiac events (e.g., torsade de pointe, sudden death, and QT interval prolongation) were noted in postmarketing cases. Assessment of causality in individual cases describing these events is difficult given the complexity of patients with HRS (i.e., underlying comorbidities, concomitant treatments, and rapid deterioration in HRS-1). Terlipressin is not known to prolong the QTc interval to a clinically relevant extent (Table 6).

Hyponatremia was frequently reported in postmarketing reports and is described in some foreign terlipressin labels.[5,6] While hyponatremia is common in cirrhotic patients, several postmarketing cases described serious complications such as seizures. The incidence of hyponatremia in terlipressin-treated patients was not greater than in the placebo groups in the clinical studies, see Section 7.6.6.

[5] Lucassin (terlipressin) [product label]. Hawthorn East VIC: Ikaria Australia Pty Ltd. August 6, 2012.
[6] Glypressin (terlipressin acetate) [product label]. Kiel Germany: Ferring GmbH. September 23, 2010.

7.4. FDA Approach to the Safety Review

FDA's safety evaluation focused on the data obtained in the CONFIRM study. As previously noted, the CONFIRM study was designed under a SPA agreement with FDA to evaluate the efficacy and safety of terlipressin and address the requirements in the FDA's 2009 Complete Response Letter. This study provides adequate data to evaluate the safety profile of terlipressin in the target patient population under current standard of care. As agreed, the Applicant also provided an integrated safety analysis that pooled safety data from the CONFIRM study and two previous phase 3 studies: OT-0401 (the original NDA) and REVERSE (2015 resubmission). The pooled data (simple pooling) from these studies were used as supportive safety data in FDA's evaluation. These data are referred to as the Integrated Summary of Safety (ISS).

FDA's safety review focused on the known and potential toxicities of terlipressin based on its mechanism of action, the larger experience with the pharmacologic class (vasopressin/ vasopressin receptor agonist) and terlipressin's postmarketing experience in other countries. FDA's review included a review of data quality, AEs, laboratory data, and vital sign data. AEs were primarily analyzed using the Medical Dictionary for Regulatory Activities (MedDRA) (version 21.0) hierarchy and by pooling similar AEs using the Standardised MedDRA Query (SMQ) or FDA MedDRA Query (FMQ). The FMQ analysis is similar to a customized MedDRA query.

Safety analyses were performed on the "treated population," defined as subjects who received at least one dose of study drug. The analysis windows used for analyses of AEs, serious adverse events (SAEs) and deaths are shown in Table 27.

Table 27. Definition of Analysis Periods for Safety Analyses

Safety Event	Analysis Population	Data Period
Adverse event	Treated patients	Between first dose and 7 days after last dose
Serious adverse event	Treated patients	Between first dose and 30 days after last dose
Death	Treated patients	Between first dose and 90 days from the start of treatment

Source: Reviewer's table
SAS version 9.4 and the Office of Computational Science table builder tool were used for most analyses; MedDRA Adverse Event Diagnosis (MAED) and JMP Clinical were also used.

SAS version 9.4 and the Office of Computational Science table builder tool were used for most analyses; MedDRA Adverse Event Diagnosis and JMP Clinical were also used.

7.5. Adequacy of the Clinical Safety Database

In all phase 3 studies, the starting dose of terlipressin acetate was 4 mg/day (1 mg every 6 hours) administrated intravenously as a bolus injection over 2 minutes. A dose increase to 8 mg was allowed if SCr had decreased, but by less than 30% from baseline. Treatment was discontinued if SCr was at or above the baseline value on Day 4 in the CONFIRM and REVERSE studies and on Day 7 in the OT-0401 study. The duration of treatment exposure in the CONFIRM study and in the pooled safety dataset is summarized in Table 28. The median duration of terlipressin exposure was about 5 days. Forty-six percent of terlipressin-treated subject had exposure greater than or equal to 6 days in the CONFIRM study. This exposure and the size of overall safety data are considered acceptable for a short-term therapy such as terlipressin.

Table 28. Duration of Exposure, Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
Parameter	**Terlipressin N=200**	**Placebo N=99**	**Terlipressin N=349**	**Placebo N=249**
Duration of treatment (units)				
Mean (SD)	6.2 (3.6)	6.0 (3.7)	6.2 (4.4)	6.0 (3.9)
Median (min, max)	5 (1, 15)	4 (1, 15)	5 (1, 25)	4 (1, 19)
Patients treated by duration, n (%)				
Any duration (at least 1one dose)	200 (100)	99 (100)	349 (100)	249 (100)
<3 days	25 (12.5)	7 (7.1)	56 (16.1)	32 (12.9)
≥3 days	175 (87.5)	92 (92.9)	293 (84.0)	217(87.2)
≥6 days	92 (46.0)	38 (38.4)	147 (42.1)	106 (42.6)
≥9 days	49 (24.5)	20 (20.2)	88 (25.2)	56 (22.5)
≥12 days	26 (13.0)	13 (13.0)	48 (13.8)	29 (11.7)

Source: Reviewer's analysis, dataset: ISS adsl
Abbreviations: ISS: integrated summary of safety; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

7.6.1. Overall Adverse Event Summary

The overall incidence of AEs was similar between the terlipressin and placebo arms. However, the incidence of SAEs up to 30 days post-treatment (the time window over which such data were generally captured) was somewhat higher in the terlipressin as compared to placebo arm. Although the incidence of death up to 30 days was similar in the two arms, the incidence of death up to 90 days was greater in the terlipressin arm as compared to the placebo arm, particularly in the CONFIRM study. Study drug discontinuations and dose reductions/interruptions due to an AE were also more common in the terlipressin arm.

Table 29. Overview of Adverse Events, Controlled Trial Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
	Terlipressin (N=200) n (%)	Placebo (N=99) n (%)	Terlipressin (N=349) n (%)	Placebo (N=249) n (%)
AEs up to 7 days post-treatment	176 (88.0)	88 (88.9)	318 (91.1)	225 (90.4)
SAEs up to 30 days post-treatment	130 (65.0)	60 (60.6)	226 (64.8)	149 (59.8)
Deaths up to 30 days post-treatment	83 (41.5)	40 (40.4)	145 (41.5)	101 (40.6)
Deaths up to 90 days from start of treatment	102 (51.0)	44 (44.4)	168 (48.1)	115 (46.2)
Discontinuation due to AE	24 (12.0)	5 (5.1)	46 (13.2)	13 (5.2)
Dose reduced/interruptions due to AE	22 (11.0)	8 (8.1)	38 (10.9)	9 (3.6)

Source: Reviewer's analysis, dataset: ISS adsl & adae
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event; ISS, integrated summary of safety

7.6.2. Deaths

In CONFIRM, all-cause mortality during treatment period and up to 90 days from the start of treatment was higher in the terlipressin arm as compared to the placebo arm. Adverse events that led to death based on the AE case report forms are shown in Table 30. As expected in this patient population, hepatic disorders was the most common cause of death in both arms; a slightly higher incidence of hepatic-related death was reported in the placebo arm. A higher frequency of fatal AEs associated with respiratory failure and sepsis and septic shock were found in the terlipressin arm. Overall, similar death findings were reported in the ISS. A higher percentage of subjects died from an AE of multiple organ dysfunction syndrome (MODS) in the previous trials (OT-0401 and REVERSE). In CONFRIM, the definition for an AE of MODS was clarified and incorporated with an assessment of CLIF-SOFA and ACLF scores. With a more objective definition of MODS, the incidence of the AE of MODS leading to death in CONFIRM was similar between the arms.

Table 30. Deaths up to Day 90 in Safety Population, CONFIRM and ISS

	CONFIRM		ISS	
Deaths	Terlipressin (N=200) n (%)	Placebo (N=99) n (%)	Terlipressin (N=349) n (%)	Placebo (N=249) n (%)
Total deaths[1]	102 (51.0)	44 (44.4)	168 (48.1)	115 (46.2)
Hepatic disorders[2]	49 (24.5)	27 (27.3)	83 (23.8)	65 (26.1)
Multiple organ dysfunction syndrome	11 (5.5)	5 (5.1)	25 (7.2)	11 (4.4)
Respiratory failure[2]	18 (9.0)	1 (1.0)	29 (8.3)	9 (3.6)
Septic shock/shock	11 (5.5)	2 (2.0)	15 (4.3)	3 (1.2)
Sepsis/sepsis syndrome	5 (2.5)	0	14 (4.0)	3 (1.2)
Acute renal failure[2]	4 (2.0)	0	9 (2.6)	8 (3.2)
Gastrointestinal hemorrhage[2]	6 (3.0)	0	6 (1.7)	2 (0.8)
Treatment-emergent deaths[3]	9 (4.5)	1 (1)	16 (4.6)	11(4.4)
Respiratory failure[2]	6 (3.0)	0	8 (2.3)	2 (0.8)
Hepatic disorder[2]	2 (1.0)	0	7 (2.0)	7 (2.8)

Source: Reviewer's analysis, ISS adsl & adae
[1] Total deaths defined as deaths occurred up to 90 days from the start of the treatment
[2] Defined as MedDRA SMQ (narrow)
[3]Treatment-emergent defined as death occurred on the same day as when the last dose of study was administrated
Abbreviations: N, number of subjects in group; n, number of deaths

The timing of deaths in the study and K-M plots of deaths are shown in Table 31 and Figure 7, respectively. Approximately 50% of deaths in both arms occurred by Day 14. In the CONFIRM study, the incidence of deaths during the treatment period was higher in the terlipressin arm as compared to the placebo arm (4.5% versus 1.0%); however, this finding was not seen in the ISS population. The most commonly reported AE leading to death during the treatment period was respiratory failure, which occurred in six of the nine subjects who died in the terlipressin arm.

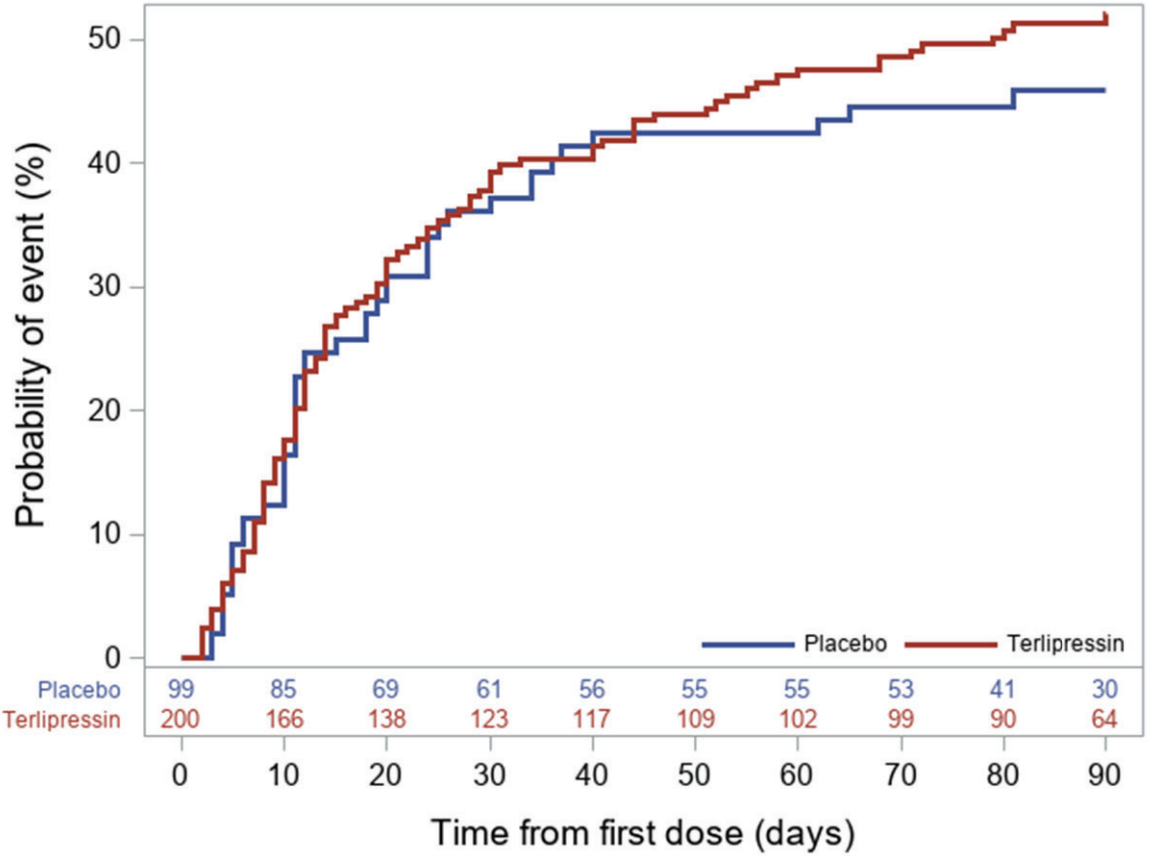
Table 31. Timing of Death up to Day 90, Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
Timing of Death	**Terlipressin (N=200)**	**Placebo (N=99)**	**Terlipressin (N=349)**	**Placebo (N=249)**
Death during study treatment period[1]	9 (4.5)	1 (1.0)	16 (4.6)	11 (4.4)
Death by Day 7	22 (11.0)	11 (11.1)	41 (11.7)	32 (12.9)
Death by Day 14	53 (26.5)	24 (24.2)	87 (24.9)	60 (24.1)
Death by Day 30	78 (39.0)	36 (36.4)	133 (38.1)	88 (35.3)
Death by Day 60	94 (47.0)	41 (41.4)	157 (45.0)	111 (44.6)
Death by Day 90[2]	102 (51.0)	44 (44.4)	170 (48.7)	120 (48.2)
Days from start of study drug to death[3]				
Median (IQR)	14 (8,30)	12 (7,25)	14 (8, 28)	15 (7-32)
Mean (SD)	23 (21)	19 (17)	22 (20)	22 (21)

Source: Reviewer's table, dataset ISS adsl & adae
[1] Defined as death occurred on same day as when last dose of study was administrated
[2] Included two deaths in CONFIRM without a date of death
[3] Included deaths up to 90 days from start of treatment; using end of study date as death data for two deaths without a date of death
Abbreviations: IQR, interquartile range; STD, standard deviation; ISS, integrated summary of safety

The K-M curves of deaths up to Day 90 show that the incidence of death was similar between the two arms through Day 40 and separated beyond that. K-M estimates of deaths by AE category are shown in Appendix III.17.1. As compared to the placebo arm, there was a higher incidence of fatal respiratory events in the terlipressin arm early in the study (80% of deaths due to respiratory failure occurred within 10 days) and a slightly higher incidence of deaths due to hepatic disorders and sepsis/septic shock later.

Figure 7. Kaplan-Meier Estimates of Death up to Da 90, Safet Population, CONFIRM Study



Source: Reviewer's analysis, dataset: ISS adsl & adae
Number of patients at risk is displayed at the bottom inside of the graph

7.6.3. Serious Adverse Events

The incidence of SAEs was slightly higher in the terlipressin arm as compared to the placebo arm in the CONFIRM study. Hepatic disorders were the most commonly reported SAEs in both arms with a slightly higher incidence in the placebo arm. There was a higher incidence of SAEs related to respiratory failure, serious infections (mainly sepsis and septic shock), GI bleeding, and abdominal pain in the terlipressin arm as compared to the placebo arm. For further discussion of these findings, see Section 7.6.5.

Table 32. Serious Adverse Events, Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
Serious Adverse Event	**Terlipressin (N=200) n (%)**	**Placebo (N=99) n (%)**	**Terlipressin (N=349) n (%)**	**Placebo (N=249) n (%)**
Any SAE	130 (65.0)	60 (60.6)	266 (64.8)	149 (59.8)
SAE AE grouping of interest in at least 5% of subjects				
Hepatic disorders[1]	50 (25.0)	33 (33.3)	91 (26.1)	74 (29.7)
Respiratory failure[1]	28 (14.0)	5 (5.1)	44 (12.6)	19 (7.6)
Infection and infestations[2]	19 (9.5)	5 (5.1)	43 (12.3)	19 (7.6)
Sepsis/septic shock[3]	14 (7.0)	0 (0.0)	30 (8.6)	6 (2.4)
Gastrointestinal haemorrhage[1]	17 (8.5)	4 (4.0)	23 (6.6)	10 (4.0)
Abdominal pain[4]	12 (6.0)	1 (1.0)	17 (4.9)	2 (0.8)
Renal injury[4]	9 (4.5)	2 (2.0)	26 (7.5)	13 (5.2)
Multiple organ dysfunction syndrome	9 (4.5)	3 (3.0)	25 (7.2)	8 (3.2)

Source: Reviewer's analysis, dataset: ISS adsl & adae
[1] Coded as Standardised MedDRA Query (narrow)
[2] Coded as MedDRA system organ class
[3] Coded with these preferred terms: sepsis, septic shock, sepsis syndrome, urosepsis, abdominal sepsis and enterococcal sepsis
[4] Coded as FMQ
Abbreviations: N, number of subjects in group; n, number of subjects with adverse event; ISS, integrated summary of safety

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Adverse events leading to permanent discontinuation of study drug were reported in a higher percentage of subjects in the terlipressin arm than in the placebo arm in the CONFIRM study. GI and respiratory disorders were the most common AEs resulting in drug withdraw in the terlipressin arm. The mean time to onset of these AEs was 3.2 and 2.4 days in the terlipressin and placebo arms, respectively. Adverse events leading to treatment withdrawal with fatal outcomes were reported for 10 (5%) subjects in the terlipressin arm and none in the placebo arm; respiratory failure/acute respiratory failure (n=5) was the most common event. Similar findings were reported for the ISS population.

Table 33. Adverse Events Leading to Discontinuation, Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
MedDRA SOC/ Preferred Term[1]	Terlipressin (N=200)	Placebo (N=99)	Terlipressin (N=349)	Placebo (N=249)
AE leading to study drug withdrawal	24 (12.0)	5 (5.1)	46 (13.2)	13 (5.2)
Gastrointestinal disorders (SOC)	9 (4.5)	1 (1.0)	16 (4.6)	3 (1.2)
Abdominal pain	3 (1.5)	0	6 (1.7)	0
Gastrointestinal hemorrhage	2 (1.0)	0	3 (0.9)	1 (0.4)
Intestinal ischemia	2 (1.0)	0	4 (1.1)	0
Abdominal pain upper	1 (0.5)	0	1 (0.3)	0
Diarrhea	1 (0.5)	0	2 (0.6)	0
Intestinal obstruction	1 (0.5)	0	1 (0.3)	0
Nausea	1 (0.5)	1 (1.0)	1 (0.3)	1 (0.4)
Vomiting	1 (0.5)	0	2 (0.6)	0
Respiratory, thoracic, and mediastinal disorders (SOC)	8 (4.0)	0	12 (3.4)	2 (0.8)
Respiratory failure	3 (1.5)	0	4 (1.1)	1 (0.4)
Acute respiratory failure	2 (1.0)	0	3 (0.9)	0
Dyspnoea	1 (0.5)	0	1 (0.3)	0
Hypoxia	1 (0.5)	0	2 (0.6)	0
Pulmonary edema	1 (0.5)	0	3 (0.9)	1 (0.4)
Tachypnoea	1 (0.5)	0	1 (0.3)	0
Vascular disorders (SOC)	5 (2.5)	1 (1.0)	7 (2.0)	3 (1.2)
Shock	2 (1.0)	0	2 (0.6)	0
Circulatory collapse	1 (0.5)	0	1 (0.3)	0
Hematoma	1 (0.5)	0	1 (0.3)	0
Hypotension	1 (0.5)	1 (1.0)	2 (0.6)	3 (1.2)

Source: Reviewer's analysis ISS data: adsl & adae
[1] Data shown if MedDRA occurs in >2% terlipressin treated subjects; select PT shown
Abbreviations: SOC, system organ class, AE, adverse event, number of subjects in treatment arm; n, number of subjects in specified population or group

7.6.5. Treatment-Emergent Adverse Events

Treatment-emergent AEs were generally consistent with the known safety profile of terlipressin and expected risks based on the drug's mechanism of action. The most common treatment-emergent AEs were respiratory and GI-related AEs. Other known risks, such as ischemia-related events, were also reported at a greater frequency in the terlipressin arm (Table 34). In addition, AEs of fluid overload were reported in a greater percentage of subjects in the terlipressin group. These events are discussed in further detail in the sections that follow.

Table 34. Adverse Event Occurring ≥2% More Often in Patients Treated With Terlipressin Than in Placebo-Treated Patients, Safety Population, CONFIRM Study

Grouped PTs	Terlipressin (N=200) n (%)	Placebo (N=99) n (%)	Risk Difference (95% CI)
Ischemia-associated events	9 (4.5)	0	4.5 (1.6, 7.4)
Respiratory disorders[1]	79 (39.5)	25 (25.3)	14.2 (3.3, 25.1)
Respiratory failure[2]	36 (18.0)	10 (10.1)	7.8 (-0.1, 15.9)
Dyspnoea	25 (12.5)	5 (5.1)	7.4 (1.1, 13.7)
Pulmonary edema	15 (7.5)	5 (5.1)	2.4 (-3.3, 8.1)
Pleural effusion	11 (5.5)	0 (0.0)	5.5 (2.3, 8.7)
Tachypnoea	6 (3.0)	1 (1.0)	2 (-1.1, 5.1)
Wheezing	6 (3.0)	1 (1.0)	2 (-1.1, 5.1)

Grouped PTs	Terlipressin (N=200) n (%)	Placebo (N=99) n (%)	Risk Difference (95% CI)
GI disorders[1]	95 (47.5)	35 (35.4)	12.1 (0.4, 23.8)
Abdominal pain	42 (21.0)	(8.1)	12.9 (5.1, 20.7)
Diarrhea	26 (13.0)	7 (7.1)	5.9 (-1.0, 12.8)
Nausea	32 (16.0)	10 (10.1)	5.9 (-1.9, 13.7)
GI hemorrhage[2]	23 (11.5)	8 (8.1)	3.4 (-3.6, 10.4)
Bradycardia	10 (5)	0	5 (2.0, 8.0)
Hemodynamic edema/effusions/ fluid overload[2]	55 (27.5)	(16.2)	11.4 (1.8, 20.8)
Fluid overload	17 (8.5)	3 (3.0)	5.5 (0.4, 10.6)

Source: Reviewer's analysis, dataset: ISS adsl & adae
This table only lists AEs likely to be treatment-related
[1] Coded as MedDRA system organ class
[2] Coded as Standardised MedDRA Query (narrow)
Abbreviations: CI, confidence interval; GI, gastrointestinal, PT, preferred term

7.6.5.1. Ischemia-Associated AEs

Terlipressin is a vasoconstrictor and can cause ischemia in various organ systems (e.g., skin, bowel, and myocardium). To assess the incidence of ischemia-associated AEs, the Applicant reviewed all reported AEs retrospectively to include relevant preferred terms from different body organ systems.

In the CONFIRM study, there were a total of nine subjects with ischemia-associated AEs (4.5%) in the terlipressin group and none in the placebo group. These events occurred early in the treatment period (range of 1 to 5 days after the first dose of terlipressin with median onset of 2.5 days). The most commonly reported ischemia-associated event was skin discoloration (n=4). Although most of these events were mild to moderate in intensity, two SAEs of intestinal ischemia were reported in the terlipressin arm. One subject developed abdominal pain on Day 3 and had evidence of a splenic infarct, diffuse bowel edema, hepatic infarct, and probable sepsis on CT scan. The subject developed an event of shock and died on the same day. The other subject developed intestinal ischemia with severe bloody bowel movements/rectal bleeding (possible severe bowel ischemia) on Day 5. A subsequent colonoscopy revealed blood in the entire colon on Day 9. The subject died on Day 11 due to an SAE of worsening hepatic failure.

In the ISS population, 25 subjects (7.2%) in the terlipressin arm and one subject (0.4%) in the placebo arm reported an ischemia-associated AE (Table 35). In the CONFIRM and REVERSE studies, the protocols required that study treatment be permanently discontinued if an event of cardiac ischemia or mesenteric ischemia occurred. More than half of these events in the terlipressin group (13/25, 52%) resulted in the drug being permanently stopped or withdrawn. The majority of the ischemia-associated AEs (17/25, 68%) recovered/resolved.

Table 35. Incidence of Ischemia-Associated AEs and SAEs, Safety Population, ISS

	Terlipressin (N=349)	Placebo (N=249)
Ischemic AEs	25 (7.2)	1 (0.4)
Skin discoloration	6 (1.7)	0
Cyanosis	5 (1.4)	0
Intestinal ischemia	4 (1.1)	0
Ischemia	2 (0.6)	0
Vascular skin disorder	2 (0.6)	0
Electrocardiogram ST segment depression	1 (0.3)	0
Electrocardiogram T wave abnormal	1 (0.3)	0
Livedo reticularis	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Peripheral coldness	1 (0.3)	0
Poor peripheral circulation	1 (0.3)	0
Raynaud's phenomenon	1 (0.3)	0
Vasoconstriction	1 (0.3)	0
Myocardial ischemia	0	1 (0.4)
Ischemic SAEs	10 (2.9)	1 (0.4)
Intestinal ischemia	4 (1.1)	0
Vascular skin disorder	2 (0.6)	0
Cyanosis	1 (0.3)	0
Livedo reticularis	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Poor peripheral circulation	1 (0.3)	0
Myocardial ischemia	0	1 (0.4)

Source: Reviewer's analysis, dataset: ISS adsl & adae
Adverse events of special interest were prespecified for abdominal pain, chest pain or dyspnea/wheezing/bronchospasm/pulmonary edema in CONFIRM and additional information on these events were collected to assess whether events were ischemia-related
Abbreviations: AE, adverse event; SAE, serious adverse event; ISS, integrated summary of safety

7.6.5.2. Respiratory Events

Terlipressin is known to cause respiratory adverse effects, likely mediated by the drug's effects on the V1a receptors (constrictive effects on smooth muscle) and V2 receptors (fluid retention).

In the CONFIRM study, the incidence of respiratory-related AEs (events in the respiratory, thoracic, and mediastinal disorder system organ class) was higher in the terlipressin arm (40%) than in the placebo arm (26%) (Table 36). The most commonly reported respiratory AEs in the terlipressin arm were respiratory failure, dyspnoea, pulmonary edema, and pleural effusion, and these events were reported at a higher incidence in the terlipressin than in the placebo arm. Most of the respiratory AEs occurred within 10 days after the first dose of study treatment with a median onset of 3 to 4 days. Whereas most of the respiratory AEs were reported to be mild to moderate in intensity, about 90% of respiratory failure events and about 30% of pulmonary edema events were reported to be severe. For respiratory failure as a serious adverse event, the treatment difference (terlipressin minus placebo) was 9%. For more information on findings related to respiratory failure and volume overload, see Sections 7.6.5.4.1 and 7.7.1, respectively.

Table 36. Incidence of Respiratory AEs, Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
SOC/Preferred Term	Terlipressin (N=200)	Placebo (N=99)	Terlipressin (N=349)	Placebo (N=249)
Respiratory, thoracic, and mediastinal disorders (SOC) AEs	79 (39.5)	25 (25.3)	149 (42.7)	71 (28.5)
Respiratory failure SMQ[1]	36 (18.0)	10 (10.1)	58 (16.6)	25 (10.0)
Dyspnoea	25 (12.5)	5 (5.1)	42 (12.0)	15 (6.0)
Pulmonary edema	15 (7.5)	5 (5.1)	29 (8.3)	14 (5.6)
Pleural effusion	11 (5.5)	0 (0.0)	19 (5.4)	5 (2.0)
Tachypnoea	6 (3.0)	1 (1.0)	6 (1.7)	2 (0.8)
Wheezing	6 (3.0)	1 (1.0)	14 (4.0)	3 (1.2)
Respiratory, thoracic, and mediastinal disorders (SOC) SAEs	33 (16.5)	8 (8.1)	57 (16.3)	26 (10.4)
Respiratory failure SMQ[1]	28 (14.0)	5 (5.1)	44 (12.6)	19 (7.6)
Respiratory failure	20 (10.0)	3 (3.0)	29 (8.3)	6 (2.4)
Acute respiratory failure	8 (4.0)	2 (2.0)	11 (3.2)	5 (2.0)
Acute respiratory distress syndrome	2 (1.0)	0	4 (1.1)	2 (0.8)
Respiratory arrest	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Respiratory distress	0 (0.0)	0 (0.0)	2 (0.6)	4 (1.6)

Source: Reviewer's analysis, dataset: ISS adsl & adae.
This table only includes AEs reported by greater than five subjects in the terlipressin group in the CONFIRM study
[1] Defined as MedDRA respiratory failure SMQ (narrow)
Abbreviations: SMQ, Standardised MedDRA Query; ISS, integrated summary of safety; SOC, system organ class; AE, adverse event; SAE, serious adverse event

7.6.5.3. Gastrointestinal Events

In addition to serious events such as mesenteric ischemia resulting from splanchnic vasoconstriction, GI AEs including abdominal pain, vomiting and diarrhea have been reported with the use of terlipressin.

In the CONFIRM study, more terlipressin-treated subjects had GI AEs as compared to placebo-treated subjects. The most common AEs were abdominal pain, nausea, and diarrhea. These events occurred soon after initiating terlipressin treatment with a median onset of 1 day (interquartile range (IQR) 1 to 3 days). With the exception of GI bleeding, most of the GI events were reported as mild to moderate in intensity and were managed symptomatically with dose reduction/discontinuation, if needed, with subsequent resolution. There were four GI bleeding AEs resulting in death; all were related to upper GI bleeding (e.g., esophageal variceal hemorrhage), a serious complication that occurs not infrequently in patients with advanced cirrhosis and for which terlipressin is sometimes used.[7] A higher incidence of lower GI hemorrhage (i.e., rectal hemorrhage, hematochezia) was observed in the terlipressin arm as compared to the placebo arm. No signal for GI bleeding was evident in the previous two studies. In summary, for GI SAEs as a whole, the treatment difference (terlipressin minus placebo) was 9%.

[7] Approved indication outside US for the treatment of bleeding esophageal varices

Table 37. Incidence of Gastrointestinal AEs and SAEs, Safety Population, CONFIRM Study and ISS

	CONFIRM		ISS	
	Terlipressin (N=200)	Placebo (N=99)	Terlipressin (N=349)	Placebo (N=249)
GI disorders AEs[1]	95 (47.5)	35 (35.4)	180 (51.6)	106 (42.6)
Abdominal pain[2]	42 (21)	8 (8.1)	80 (22.9)	33 (13.3)
Diarrhea	26 (13.0)	7 (7.1)	53 (15.2)	14 (5.6)
Nausea	32 (16)	10 (10.1)	52 (14.9)	29 (11.7)
Vomiting[2]	21 (10.5)	11 (11.1)	39 (11.2)	18 (7.2)
GI haemorrhage[3]	23 (11.5)	8 (8.1)	37 (10.6)	20 (8.0)
GI disorders SAEs[1]	30 (15)	6 (6.1)	48 (13.8)	18 (7.2)
GI haemorrhage[3]	17 (8.5)	4 (4.0)	23 (6.6)	10 (4.0)
Abdominal pain[2]	12 (6)	1 (1)	17 (4.9)	2 (0.8)
Diarrhea	1 (0.5)	0	1 (0.3)	0
Nausea	1 (0.5)	0	2 (0.6)	0
Vomiting[2]	3 (1.5)	0	4 (1.2)	0

Source: Reviewer's analysis, dataset: ISS adsl & adae
[1] Coded as MedDRA system organ class
[2] Coded as FDA MedDRA Query
[3] Coded as Standardised MedDRA Query (narrow)
Abbreviations: AE, adverse event; SAE, serious adverse event; GI, gastrointestinal; ISS, integrated summary of safety

7.6.5.4. Other Safety Signals

7.6.5.4.1. Edema and Fluid Overload

An FDA analysis of MedDRA SMQs revealed a higher incidence of AEs in the terlipressin arm as compared to the placebo arm for the MedDRA SMQ of "hemodynamic edema, effusions and fluid overload" in the CONFIRM study. The majority of these AEs were reported to be mild to moderate in severity; however about 40% of these events in the terlipressin arm did not recover/resolve during the follow-up period. The most concerning fluid overload AE was pulmonary edema. More than 80% of pulmonary edema AEs in the terlipressin arm in the CONFIRM study were of moderate to severe intensity; one was reported as having a fatal outcome. All pulmonary edema AEs in the terlipressin arm occurred within 7 days of initiating study drug with a median onset of 4 days (IQR: 3 to 4 days). Overall, there was a 3% difference in edema and fluid overload SAEs (terlipressin minus placebo).

Table 38. Incidence of AEs and SAEs Related to Edema and Fluid Overload, Safety Population, CONFIRM Study and ISS

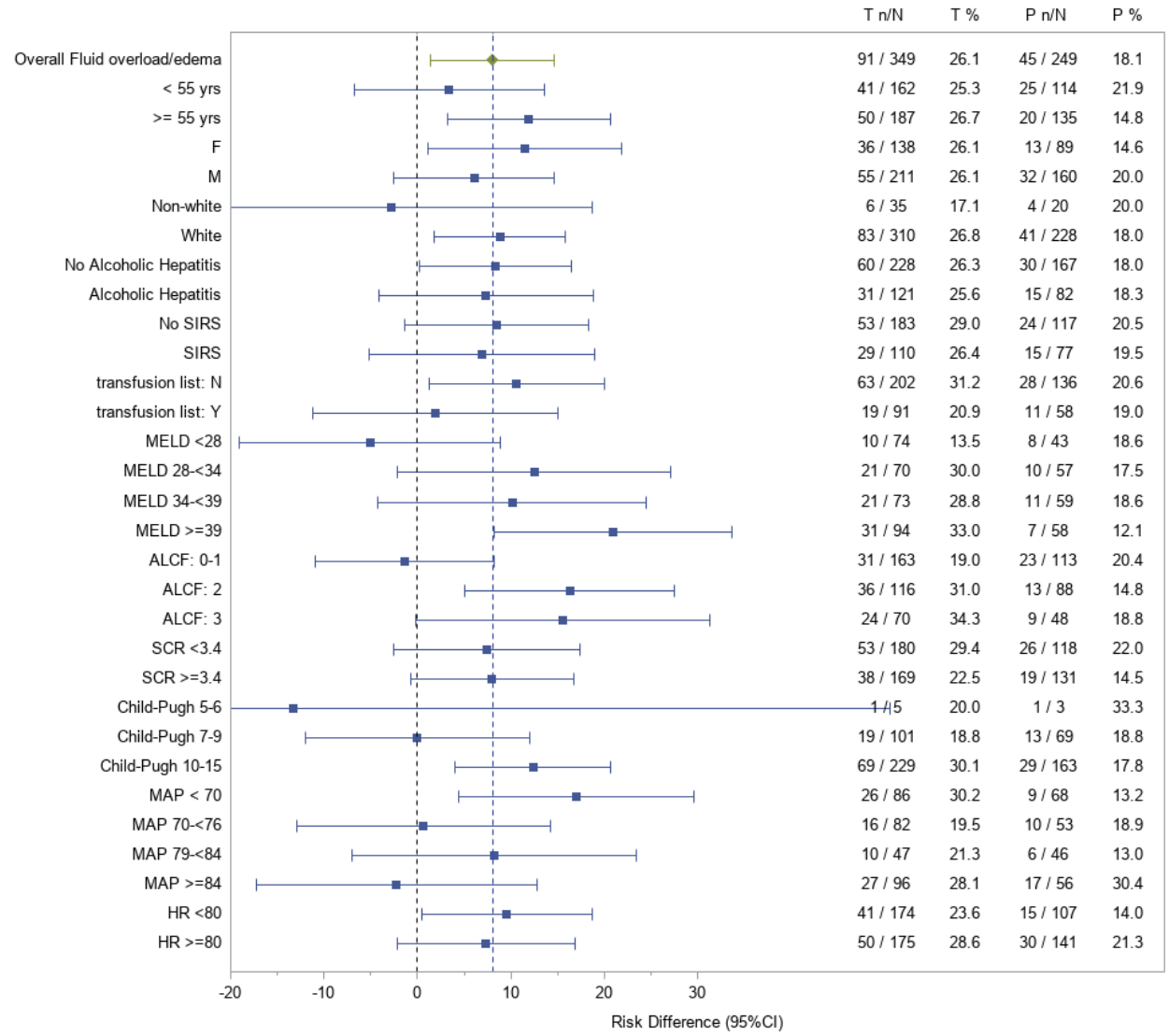
	CONFIRM		ISS	
	Terlipressin (N=200)	Placebo (N=99)	Terlipressin (N=349)	Placebo (N=249)
Hemodynamic edema, effusions, and fluid overload (SMQ) AEs	55 (27.5)	16 (16.2)	91 (26.1)	45 (18.1)
Fluid overload	17 (8.5)	3 (3.0)	28 (8.0)	9 (3.6)
Pulmonary edema	15 (7.5)	5 (5.1)	29 (8.3)	14 (5.6)
Pleural effusion	11 (5.5)	0	19 (5.4)	5 (2.0)
Ascites	10 (5.0)	3 (3.0)	10 (2.9)	9 (3.6)
Edema peripheral	6 (3.0)	3 (3.0)	14 (4.0)	12 (4.8)
Hypervolemia	3 (1.5)	0	4 (1.1)	0
Edema	3 (1.5)	1 (1.0)	5 (1.4)	5 (2.0)
Generalized edema	1 (0.5)	2 (2.0)	2 (0.6)	3 (1.2)
Joint swelling	1 (0.5)	0	1 (0.3)	0
Pericardial effusion	1 (0.5)	0	1 (0.3)	0
Acute pulmonary edema	0	0	1 (0.3)	0
Brain edema	0	0	1 (0.3)	0
Lymphedema	0	0	1 (0.3)	0
Peripheral swelling	0	0	0	1 (0.4)
Hemodynamic edema, effusions, and fluid overload (SMQ) SAEs	10 (5.0)	2 (2.0)	16 (4.6)	9 (3.6)
Fluid overload	2 (1.0)	0	2 (0.6)	0
Pulmonary edema	2 (1.0)	1 (1.0)	7 (2.0)	3 (1.2)
Ascites	3 (1.5)	0	4 (1.1)	3 (1.2)
Pleural effusion	1 (0.5)	0	0	2 (0.8)
Edema peripheral	1 (0.5)	0	1 (0.3)	0
Peripheral swelling	1 (0.5)	1 (1.0)	1 (0.3)	1 (0.4)

Source: Reviewer's analysis, dataset: ISS adsl & adae
Abbreviations: AE, adverse event; SAE, serious adverse event; ISS, integrated summary of safety; SMQ, Standardised MedDRA Query

Subgroup analyses of fluid overload–related AEs were performed using the ISS data. Overall, the results were consistent across most of the subgroups with an overall risk difference (RD) of 8.0 (95% confidence interval (CI): 1.4-14.6), favoring placebo. As shown in the figure below, subgroups that appeared to be at greater risk included those with a MELD ≥39 (RD: 20.9 [95% CI: 8.3-33.6]), ACLF Grade 2 and Grade 3 liver failure (RD: 16.3 [95% CI: 5.0-27.5] and 15.5 [95% CI: -0.1-31.2], respectively) and MAP <70 mm Hg (RD: 71.0 [95% CI: 4.4-29.6]).

Although baseline diuretic use was similar in the two arms, the numbers of patients with concomitant use of diuretics in the terlipressin arm (25.5%) was approximately twice that in the placebo arm (13.1%) during the CONFIRM study.

Figure 8. Subgroup Analysis for Fluid Overload–Related AEs, Safety Population, ISS



Source: Reviewer's analysis, dataset: ISS adsl, adae, adlb, adsaf & tte1
Abbreviations: MELD, model for end-stage liver disease; SIRS, systemic inflammatory response syndrome; ALCF: acute-on-chronic liver failure; SCR, serum creatinine; MAP, mean arterial pressure; HR: Heart rate; CI, confidence interval; ISS, integrated summary of safety; F, female; M, male

7.6.5.4.2. Serious Infection

Patients with decompensated cirrhosis and advance ACLF are at high risk for infection.

In the CONFIRM study, the incidence of infection and infestation SAEs was higher in the terlipressin arm than in the placebo arm. The difference was largely due to a higher incidence of SAEs related to sepsis and septic shock; about 60% of these patients (8/14) died due to the event. Sepsis and septic shock SAEs occurred evenly throughout the study with a median onset of 12 days (IQR: 10 to 26 days). Five of the 14 patients with sepsis/septic shock also had a preceding respiratory failure event; for these patients, most of the events occurred in the setting of pneumonia in the presence of fluid overload.

The imbalance in sepsis/septic shock SAEs was also observed in the OT-0401 and REVERSE studies. The mechanistic basis for such a risk is not immediately clear and review of the narratives did not provide further insight into whether or how terlipressin might increase the risk of such events.

Table 39. Incidence of Infection-Related AEs and SAEs

	CONFIRM		ISS	
	Terlipressin (N=200)	Placebo (N=99)	Terlipressin (N=349)	Placebo (N=249)
Infection and infestations[1] AEs	39 (19.5)	20 (20.2)	89 (25.5)	53 (21.3)
Infection and infestations[1] SAEs	19 (9.5)	5 (5.1)	43 (12.3)	19 (7.6)
Sepsis/septic shock[2]	14 (7.0)	0	30 (8.6)	6 (2.4)

Source: Reviewer's analysis, dataset: ISS adsl & adae
[1] MedDRA system organ class
[2] Coded with these preferred terms: sepsis, septic shock, sepsis syndrome, urosepsis, abdominal sepsis and enterococcal sepsis
Abbreviations: AE, adverse event; SAE, serious adverse event, ISS, integrated summary of safety

Terlipressin is not known to alter immune responses in animals. In cases with available culture results, the etiologic agents were predominantly bacterial. It is possible that terlipressin played a role by contributing to fluid overload and/or abdominal ischemia. However, based on the available data, the role of terlipressin in these sepsis events is unclear.

7.6.5.4.3. Bradycardia

Terlipressin is known to increase MAP and decrease HR. Bradycardia AEs were reported in 10 subjects (5%) in the terlipressin group and none in the placebo group in the CONFIRM study. The majority of the events (8/10, 80%) were reported to be mild to moderate in intensity and resolved on-treatment. The findings for bradycardia AEs in the ISS population were consistent with those in CONFIRM (incidence of 6.5% versus 0.8% in the terlipressin and placebo group, respectively). None of the bradycardia AEs in the CONFIRM study or ISS population was categorized as an SAE.

7.6.6. Laboratory Findings

Analyses of laboratory data from the CONFIRM study did not raise major safety concerns. Median changes from baseline to the end of treatment were similar between the arms for the majority of clinical chemistry and hematology parameters collected in the study. Subjects in the terlipressin arm had a greater increase in glucose levels from baseline (median change from baseline of 10 mg/dL and 2 mg/dL in the terlipressin and placebo arms, respectively). A greater percentage of subjects in the terlipressin arm also met the abnormality criteria for glucose levels during the study (see table below) and reported AEs of hyperglycemia and blood glucose increases (six subjects in the terlipressin arm; none in the placebo arm). Such findings are consistent with the known effects of vasopressin on hepatic glycogenolysis.

Electrolytes abnormalities such as hyponatremia and hypokalemia have been reported in the postmarketing setting and/or listed in foreign labels. The percentage of subjects meeting the abnormality criteria for these parameters is shown in Table 40. The incidence of hyponatremia was similar in the two treatment arms. In the terlipressin arm, a higher percentage of subjects had potassium levels less than 3 mmol/L and a lower percentage had potassium levels >5, but a similar percentage of subjects reported AEs of hypokalemia in both arms (7.5% in the terlipressin arm and 7.1% in the placebo arm).

Table 40. Patients Meeting Laboratory Abnormality Criteria, From Baseline Through End of Treatment, Safety Population, CONFIRM Study

	Terlipressin n (%)	Placebo n (%)
Glucose	N=188	N=93[1]
>150 mg/dL	81 (43.1)	22 (23.7)
>150 mg/dL and 30% increase from baseline	53 (28.2)	15 (16.1)
Sodium	N=195[1]	N=97[1]
>150 mmol/L	11 (5.6)	4 (4.1)
<130 mmol/L	45 (23.1)	25 (25.8)
Potassium	N=194[1]	N=97[1]
>5 mmol/L	18 (9.3)	17(17.5)
<3 mmol/L	37 (19.1)	4 (4.1)

Source: Reviewer's analysis, dataset: ISS adsl & ad b
[1] Number of subjects who had a baseline measure and at least one postbaseline measure
Abbreviations: N, number of subjects; n, number of subjects with abnormality

Overall, the laboratory findings in the CONFIRM study were consistent with the findings in the REVERSE and OT-0401 studies.

7.6.7. Vital Sign Findings

Vital signs were measured at baseline and daily during the treatment at several time points (i.e., predose, 5 minutes postdose, and 2 hours postdose). As would be expected given terlipressin's mechanism of action, increases in MAP and decreases in HR were observed following the administration of terlipressin in the CONFIRM study; these effects were most apparent on Day 1 (Table 41). At the end of treatment, median increases in MAP were approximately 5 and 0.7 mm Hg in the terlipressin and placebo arms, respectively. Median changes in HR from baseline to the end of treatment were similar between the two arms. Overall, vital sign findings in the CONFIRM study were consistent with those reported in the previous studies.

Table 41. Changes of Vital Signs From Baseline at Day 1 and End of Treatment, Safety Population, CONFIRM Study

Vital Signs/Timepoint	Parameter	Terlipressin	Placebo
Mean arterial pressure (mmHg)			
Day 1	N	193	97
2 hours postdose[1]	Median (IQR)	8.5 (3.3,14.2)	0 (-4,4.7)
End of treatment	N	200	99
Last measurement	Median (IQR)	5 (-3.2,13.7)	0.7 (-8.3, 5.3)
Heart rate (bpm)			
Day 1	N	191	97
2 hours postdose[1]	Median (IQR)	-6.5 (-13, -2)	1 (-2.5, 5)
End of treatment	N	200	99
Last measurement	Median (IQR)	2 (-8, 12)	2 (-4,12)

[1] Similar results were found for 5 minutes postdose
Source: Review's analysis, dataset: ISS adsl & advs
Abbreviations: IQR, interquartile range; bpm, beats per minute

As compared to subjects in the placebo arm, a greater percentage of subjects in the terlipressin arm met the abnormality criteria for vital signs during the study (see Table 42). The percentage of subjects reporting AEs of hypertension and blood pressure increase was similar in the two arms (3% in the terlipressin arm and 2% in the placebo arm). See Section 7.6.5.4.3 for further discussion of bradycardia.

Table 42. Patients Meeting Vital Sign Abnormality Criteria, From Baseline Through End of Treatment, Safety Population, CONFIRM Study

	Terlipressin N=200 n (%)	Placebo N=99 n (%)
MAP increase		
>30 mm Hg increase	60 (30.0)	15 (15.2)
>30 mm Hg increase and MAP >100 mm Hg	52 (26.0)	13 (13.1)
HR decrease		
<20 bpm drop	67 (33.5)	13 (13.1)
<20 bmp drop and HR <60 bpm	28 (14.0)	1 (1.0)

Source: Review's analysis, dataset: ISS adsl & advs
Abbreviations: MAP, mean arterial pressure; HR, heart rate

7.7. Review Issues Relevant to the Evaluation of Risk

7.7.1. Respiratory Failure

Issue

The greater incidence of SAEs of "respiratory failure" in the terlipressin as compared to the placebo arm is a significant safety concern. Whether this serious risk can be adequately addressed by the proposed risk mitigation strategy was an important review issue.

Assessment

Respiratory Failure Serious Adverse Events

A higher incidence of respiratory failure SAEs was reported in the terlipressin arm as compared to the placebo arm (14% versus 5.1%, RD =8.9 [2.4, 15.4]) in the CONFIRM study. Although the protocol/case report form did not contain a prespecified definition of "respiratory failure" or otherwise specify what should be considered a serious respiratory event, reviewing the narratives for these events supports the clinical significance of the events (see Appendix III.17.2 for narratives for the 28 patients with SAEs of respiratory failure in the terlipressin arm). The interventions required for these respiratory failure SAEs are summarized in Table 43. The majority of these events required an intervention such as intubation or the use of bilevel positive airway pressure (BiPAP). For patients who were not intubated (n=9), most of them (6/9, 67%) were put on comfort care and died shortly after the event.

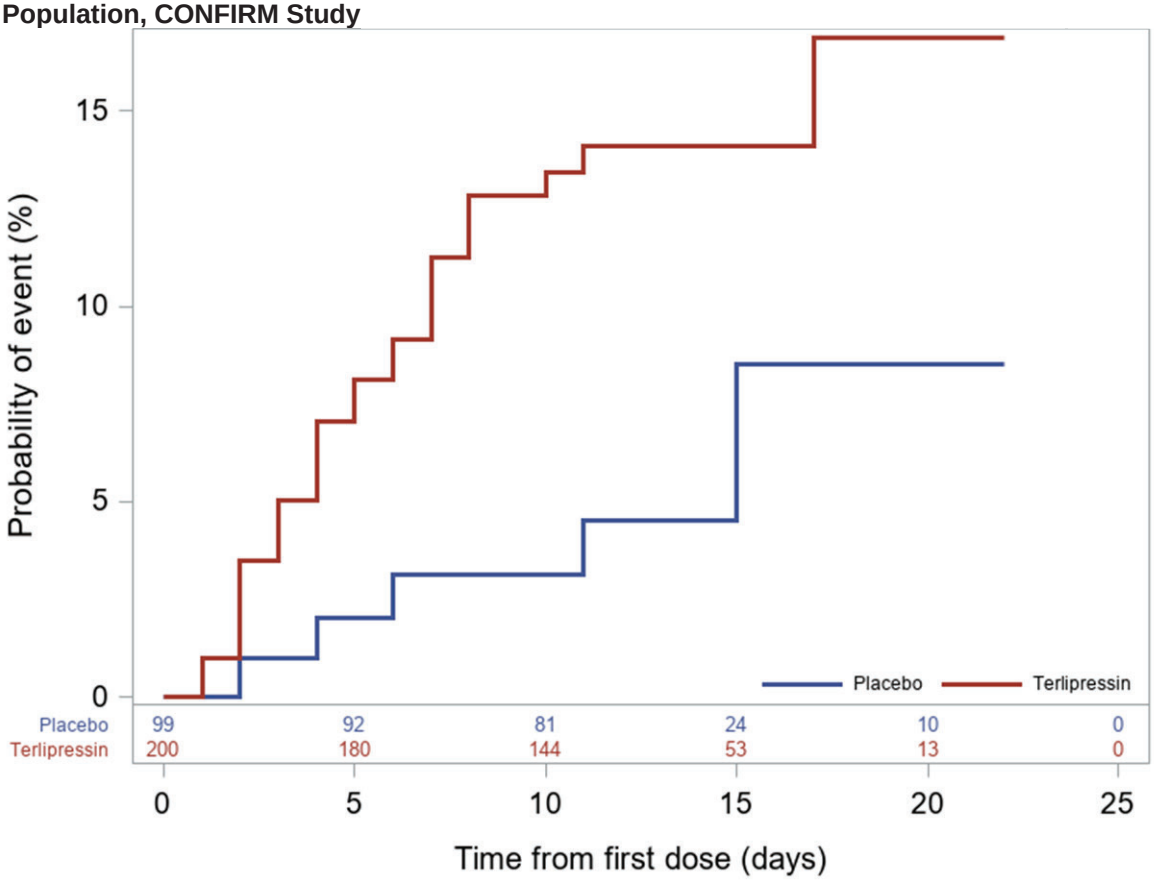
Table 43. Interventions for Respiratory Failure SAEs, Safety Population, CONFIRM Study

	Terlipressin (N=200)	Placebo (N=99)	Risk Difference (%)
Respiratory failure SAE	28 (14.0%)	5 (5.1%)	8.9
Respiratory failure SAE with intubation or BiPAP	23 (11.5%)	4 (4.0%)	7.5
Respiratory failure SAE with intubation	19 (9.5%)	4 (4.0%)	5.5
Respiratory failure SAE with intubation or comfort care	25 (12.5%)	5 (5.1%)	7.4

Source: Review's analysis, dataset: ISS adsl & adae
Abbreviations: BiPAP, bilevel positive airway pressure; SAE, serious adverse event

The majority of the serious respiratory failure events in the terlipressin arm occurred on treatment and within 10 days with a median onset of 4.5 days (IQR: 2 to 7 days). Two events occurred on the day the first dose of terlipressin was administered. The K-M curves of respiratory SAEs demonstrated an early separation between the arms (Figure 9), strongly suggesting causality of terlipressin.

Figure 9. Kaplan-Meier Estimates of Respiratory Failure Serious Adverse Events, Safety Population, CONFIRM Study

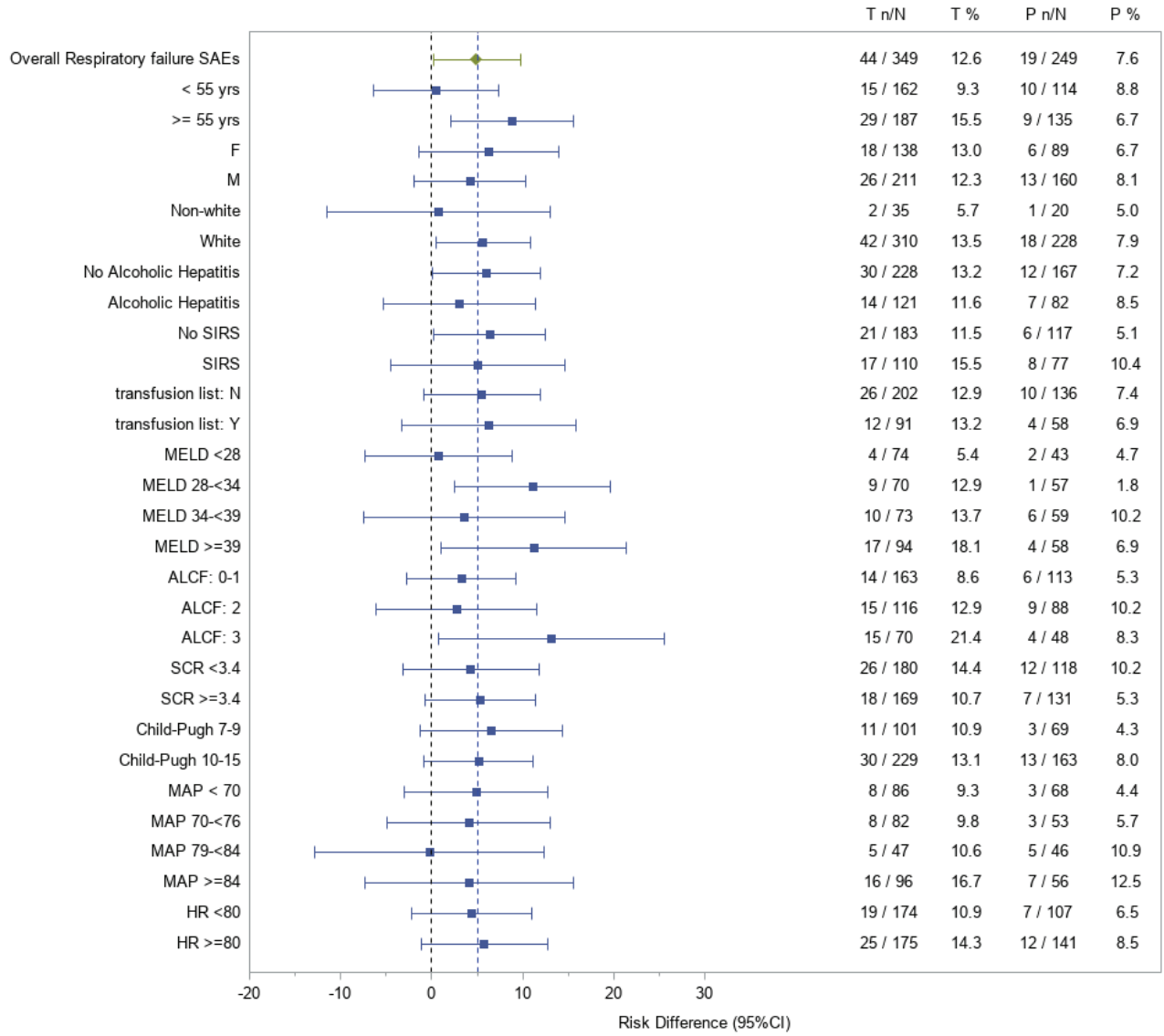


Source: Reviewer's analysis ISS data: adsl & adae

The outcome of these events was concerning. Sixty-one percent of these events (17/28) in the terlipressin arm resulted in death, while one fatal respiratory failure event was reported in the placebo arm (1/5, 20%).

Using the ISS data, subgroup analyses of respiratory failure SAEs were explored. Overall, the results were consistent across most of the subgroups with an overall RD of 5.0 (95% CI: 0.2-9.8) favoring the placebo arm. The risk of developing respiratory failure SAEs was higher in subjects with advanced disease, as demonstrated among subjects with baseline MELD ≥39 (RD: 11.2 [95% CI: 1.0-21.3]) and ACLF Grade 3 liver failure (RD: 13.1 [95% CI: 0.7-25.5]) as well as older patients (age ≥55 years old). A higher risk observed among subjects with MELD 28-<34 was mainly due to a very low incidence of the event in the placebo arm. In both treatment arms, the incidence of respiratory failure SAEs was high among subjects with SIRS and higher baseline MAP (i.e., ≥84 mm Hg), higher baseline HR (i.e., ≥80 bpm) and lower baseline SCr (i.e., <3.4 mg/dl); however, the RD remained similar across these subgroups.

Figure 10. Subgroup Analysis for Respiratory Failure Serious Adverse Events, Safety Population, ISS



Source: Reviewer's analysis, dataset: ISS adsl, adae, adlb, adsaf & tte1
Abbreviations: MELD, model for end-stage liver disease; SIRS, systemic inflammatory response syndrome; ALCF, acute-on-chronic liver failure; SCR, serum creatinine; MAP, mean arterial pressure; HR, heart rate; ISS, integrated summary of safety; CI, confidence interval; F, female; M, male

Respiratory Failure and Fluid Overload in the Setting of Albumin Loading

The incidence and severity of respiratory failure AEs were assessed in all phase 3 studies (Table 44), keeping in mind the well known limitations of cross-trial comparisons. No signal for respiratory failure was evident in the first study (OT-0401). In the second study (REVERSE), there was a trend towards a greater frequency of respiratory failure AEs in the terlipressin arm, but no trend for SAEs. In the CONFIRM study, trends were evident in both SAEs and all AEs.

Overall, the incidence and severity of respiratory failure AEs increased over time in the terlipressin arm across the three studies (CONFIRM > REVERSE > OT-0401); the same trend was not observed in the placebo arm (Table 44).

Table 44. Incidence and Severity of Respiratory Failure AEs and SAEs Across Studies

	OT-0401		REVERSE		CONFIRM	
	Placebo (N=55)	Terlipressin (N=56)	Placebo (N=95)	Terlipressin (N=93)	Placebo (N=99)	Terlipressin (N=200)
Respiratory failure AEs	5 (9.1)	6 (10.7)	10 (10.5)	16 (17.2)	10 (10.1)	36 (18.0)
Severe	4 (7.3)	5 (8.9)	7 (7.4)	9 (9.7)	6 (6.1)	32 (16.0)
Moderate	0	1 (1.8)	2 (2.1)	5 (5.4)	1 (1.0)	4 (2.0)
Mild	1 (1.8)	1 (1.8)	1 (1.1)	4 (4.3)	3 (3.0)	1 (0.5)
Respiratory failure SAEs	5 (9.1)	6 (10.7)	9 (9.5)	10 (10.8)	5 (5.1)	28 (14.0)
Fatal	3 (5.5)	3 (5.4)	5 (5.3)	7 (7.5)	1 (1.0)	17 (8.5)
Recovered/resolved	1 (1.8)	1 (1.8)	2 (2.1)	2 (2.2)	1 (1.0)	10 (5.0)
Not recovered/not resolved	0	0	2 (2.1)	0	3 (3.0)	2 (1.0)
Recovered/resolved with sequelae	0	0	0	1 (1.1)	0	0
Recovering/resolving	1 (1.8)	2 (3.6)	0	0	0	0

Source: Reviewer's analysis, dataset: ISS adsl & adae
Subjects could have more than one event under respiratory failure AEs or SAEs
Abbreviations: AE, adverse event; SAE, serious adverse event

Over the course of the clinical development program for terlipressin, the use of albumin became part of the standard of care for treatment of HRS, such that nearly all (99% to 100%) subjects received prior albumin in the CONFIRM and REVERSE studies, the two studies conducted later in the development program. Similarly, mean total prior albumin exposure increased between the REVERSE and CONFIRM studies. It is possible that the additional fluid load associated with albumin use may have contributed to the observed incidence and severity of respiratory failure events in terlipressin-treated patients in CONFIRM.

More fluid overload-related adverse events were reported in the terlipressin group than the placebo group with a risk difference of 12% in CONFIRM (see Section 7.6.5.4.1). Review of the narratives of the respiratory failure SAEs showed that many events occurred in patients with an overall worsening medical condition in the setting of aspiration pneumonia/pneumonia, pulmonary edema, or fluid overload. Thirty-nine percent of the subjects who experienced serious respiratory failure also reported an AE related to fluid overload during the study.

In all three studies, the frequency of fluid overload-related AEs was greater in the terlipressin arm than in the placebo arm. The overall frequencies were greater in the REVERSE and CONFIRM studies than in the OT-0401 study (Table 45).

Table 45. Incidence and Severity of Fluid Overload–Related Adverse Events Across Studies

	OT-0401		REVERSE		CONFIRM	
	Placebo (N=55)	Terlipressin (N=56)	Placebo (N=95)	Terlipressin (N=93)	Placebo (N=99)	Terlipressin (N=200)
Haemodynamic edema, effusions, and fluid overload (SMQ)	6 (10.9)	9 (16.1)	23 (24.2)	27 (29.0)	16 (16.2)	55 (27.5)
Mild	2 (3.6)	5 (8.9)	12 (12.6)	8 (8.6)	7 (7.1)	13 (6.5)
Moderate	3 (5.5)	3 (5.4)	12 (12.6)	20 (21.5)	7 (7.1)	38 (19.0)
Severe	1 (1.8)	2 (3.6)	2 (2.1)	2 (2.2)	2 (2.0)	9 (4.5)

Source: Reviewer's analysis, dataset: ISS adsl & adae
Abbreviation: SMQ, Standardised MedDRA Query

In analyses of the ISS data, there appeared to be a relationship between prior albumin exposure (i.e., use prior to baseline) and the incidence of respiratory failure SAEs in the terlipressin arm; a similar trend was not observed in the placebo arm. Overall, the risk of respiratory failure SAEs

was higher in the terlipressin arm as compared to the placebo arm among subjects with greater albumin exposure prior to study treatment.

Table 46. Incidence of Respiratory Failure SAEs by Total Prior Albumin Exposure, ISS

Total Prior Albumin Exposure	Terlipressin n/N (%)	Placebo n/N (%)	RD (95% CI)
Overall respiratory failure SAEs	44/349 (12.6)	19/249 (7.6)	5.0 (0.2, 9.8)
Albumin <175g	6/55 (10.9)	6/58 (10.3)	0.6 (-11, 11.9)
Albumin 175 g to <300g	11/90 (12.2)	4/51 (7.8)	4.4 (-5.6, 14.4)
Albumin 300 g to <423g	11/85 (12.9)	3/53 (5.7)	7.3 (-2.2, 16.7)
Albumin ≥423g	13/79 (16.5)	4/52 (7.7)	8.8 (-2.2, 19.7)

Source: Reviewer's analysis, dataset: ISS adsl & adae
Abbreviations: SAE, serious adverse event; ISS, integrated summary of safety; CI, confidence interval

The CONFIRM protocol contained instructions for monitoring respiratory symptoms such as dyspnea, evaluating the presence of pulmonary edema, and managing fluid overload during treatment. Recommendations for management included reducing or discontinuing the dose of albumin. Despite these recommendations, the risk of respiratory failure SAEs (terlipressin arm relative to placebo) tended to be greater in CONFIRM than in the prior studies.

Discussions with the Applicant

On May 29, 2020, the review team issued a General Advice letter to the Applicant identifying SAEs of respiratory failure and AEs of fluid overload as substantive review issues that warranted further discussion. The Applicant shared their initial thinking on a risk mitigation strategy at a follow-up teleconference held on June 4, 2020, and later expanded upon and revised their proposal in their briefing document and presentation for the Terlipressin Advisory Committee Meeting. Following the Advisory Committee Meeting, and in response to an FDA request, the Applicant formally submitted their proposed risk migration plan to the FDA, along with information on the expected effect of the aggregate strategy on efficacy outcomes.

At this time, the Applicant's proposed risk mitigation strategy includes the following components:

1. To reduce the incidence of, and mortality from, serious respiratory failure in patients on terlipressin, the Applicant is proposing to include respiratory failure in Section 5 Warnings and Precautions in labeling. The proposed language includes the following:
    a. Do not administer terlipressin in patients with pulmonary edema, pneumonia, dyspnea, or tachypnea until these events are adequately addressed or resolved. Due to the risk of aspiration, patients with worsening hepatic encephalopathy (West Haven classification Stage ≥3) should be treated and the airway protected as clinically indicated.
    b. Patients with ACLF Grade 3 are at significant risk for serious or fatal respiratory failure. Use of terlipressin in these patients should be considered only when the anticipated benefit to the patient outweighs the potential risk.
    c. Fluid overload should be closely monitored during treatment with terlipressin. Manage fluid overload by reducing or discontinuing the administration of albumin and other fluids and judicious use of diuretics. If fluid overload persists, temporarily interrupt, reduce, or discontinue terlipressin treatment.
    d. Immediately interrupt terlipressin dosing in the setting of treatment-emergent pulmonary edema, new onset or worsening pneumonia, and unresolved hepatic

encephalopathy ≥ Grade 3 with risk of aspiration. Terlipressin may be restarted upon resolution of these events.

2. To improve the overall benefit-risk profile of terlipressin, the Applicant is proposing to include "increased mortality in patients with serum creatinine ≥ 5 mg dL" in Section 5 Warnings and Precautions in labeling. The Applicant recommends that use of terlipressin in patients with SCr ≥ 5 mg/dL should be considered only when the anticipated benefit to the patient outweighs the potential risk.

The rationale for the proposed risk mitigation strategy and potential impact on key safety and efficacy results are discussed below.

Impact of Risk Mitigation Strategy on Safety and Efficacy Findings in CONFIRM

Baseline ACLF Grade 3 was a predictor of respiratory failure SAEs in post hoc subgroup analyses of data from CONFIRM and the ISS. The incidence of respiratory failure SAEs and fatal respiratory failure events is summarized in the table below. Twelve of the 28 SAEs (43%) of respiratory failure in the terlipressin group occurred in subjects with ACLF Grade 3, a subpopulation that represents 20% of the overall study population (58/299 subjects). Half of the fatal respiratory failure events occurred in subjects with ACLF Grade 3.

Table 47. Incidence of Respiratory Failure SAEs and Fatal Respiratory Failure Events by ACLF Status at Baseline, Safety Population, CONFIRM Study

	ACLF Grade (0-2)		ACLF Grade 3		Total	
	Placebo (N=81)	Terlipressin (N=160)	Placebo (N=18)	Terlipressin (N=40)	Placebo (N=99)	Terlipressin (N=200)
Respiratory failure SAE	5 (6.2)	15 (9.4)	0	12 (30.0)	5 (5.1)	28 (14.0)
Fatal respiratory failure	1 (1.2)	8 (5.0)	0	9 (22.5)	1 (1.0)	17 (8.5)

Source: Reviewer's analysis, dataset: adsl, adae & agrp.
Abbreviations: SAE, serious adverse event; ACLF, acute-on-chronic liver failure

In addition to ACLF, the proposed mitigation strategy also includes exclusion of patients with SCr ≥5 mg/dL and clinical mitigation to manage patients prior to and during treatment. Based on post hoc analyses, potential effects of the risk mitigation strategy on key safety results are summarized in the Table 48. Applying the objective components of the risk mitigation strategy (exclusion of subjects with ACLF Grade 3 or SCr ≥ 5 mg/dL at baseline) to the trial data appears to improve the risk profile for respiratory failure SAEs and overall mortality; both effects were predominantly driven by the ACLF factor. The impact on other terlipressin-related SAEs is modest. Application of the full mitigation strategy (i.e., limiting the analysis to subjects with ACLF 0-2 and SCr < 5 mg/dL, and removing an additional 11 subjects based on clinical mitigation), results in a greater reduction in respiratory failure SAEs and mortality in the terlipressin group.

Table 48. Incidence of Key Safety Results With or Without Mitigation, Safety Population, CONFIRM Study

	CONFIRM Overall Safety Population		With Mitigation for Appropriate Subjects (ACLF Grade 0-2, SCr < 5)		With Full Clinical Mitigation and Appropriate Subjects (ACLF Grade 0-2, SCr < 5)	
	Placebo N=99 n(%)	Terlipressin N=200 n(%)	Placebo N=74 n(%)	Terlipressin N=142 n(%)	Placebo N=74 n(%)	Terlipressin N=131 n(%)
Any SAEs of interest	**7 (7.1)**	**57 (28.5)**	**7 (9.5)**	**34 (23.9)**	**7 (9.5)**	**23 (17.6)**
Respiratory failure SAEs	5 (5.1)	28 (14.0)	5 (6.8)	15 (10.6)	5 (6.8)	6 (4.6)
Sepsis/septic shock SAEs	0 (0)	14 (7.0)	0 (0)	10 (7.0)	0 (0)	5 (3.8)
Abdominal pain SAEs	1 (1.0)	13 (6.5)	1 (1.4)	8 (5.6)	1 (1.4)	8 (6.1)
Edema/fluid overload SAEs	2 (2.0)	10 (5.0)	2 (2.7)	7 (4.9)	2 (2.7)	6 (4.6)
Ischemia-related SAEs	0 (0)	2 (1.0)	0 (0)	1 (0.7)	0 (0)	1 (0.8)
Death up to 90 days	44 (44.4)	102 (51.0)	32 (43.2)	63(44.4)	32 (43.2)	53 (40.5)
Fatal respiratory failure SAEs	1 (1.0)	17 (8.5)	1 (1.4)	7 (4.9)	1 (1.4)	2 (1.5)

Source: Reviewer's analysis, dataset: adsl, adae & agrp.
Abbreviations: ACLF, acute-on-chronic liver failure; SAE, serious adverse event

Based on post hoc application of the proposed risk mitigation strategy, key efficacy outcomes are summarized in Table 49. The effect of terlipressin therapy on verified HRS reversal is preserved when the mitigation strategy (i.e., full or only objective mitigation baseline criteria of ACLF 0-2 and SCr < 5 mg/dL) is applied to the trial data. Other clinical outcomes possibly predicted by the surrogate are also numerically greater in the terlipressin group compared to the placebo group. The proportion of subjects who received liver transplant among those who were on the list at any point remains lower in the terlipressin group relative to the placebo group. In sum, application of the mitigation strategy to the trial data does not appear to alter the efficacy findings.

Table 49. Key Efficacy Results With or Without Mitigation, ITT Population, CONFIRM Study

	CONFIRM Overall ITT Population		With Mitigation for Appropriate Subjects (ACLF Grade 0-2, SCr < 5)		With Full Clinical Mitigation and Appropriate Subjects (ACLF Grade 0-2, SCr < 5)	
	Placebo N=101 n(%)	Terlipressin N=199 n(%)	Placebo N=75 n(%)	Terlipressin N=141 n(%)	Placebo N=75 n(%)	Terlipressin N=130 n(%)
Verified HRS reversal	16 (15.8)	58 (29.1)	13 (17.3)	49 (34.8)	13 (17.3)	48 (36.9)
Clinical outcome possibly predicted by surrogate (Day 90)						
Alive	54 (53.5)	96 (48.2)	42 (56.0)	80 (56.7)	42 (56.0)	79 (60.8)
No RRT	62 (61.4)	141(70.9)	50 (66.7)	101 (71.6)	50 (66.7)	95 (73.1)
Alive post liver transplant	27/29 (93.1)	46/46 (100)	18/19 (94.7)	40/40 (100)	18/19 (94.7)	39/39 (100)
No RRT post liver transplant	16/29 (55.2)	37/46 (80.4)	8/19 (42.1)	23/40 (57.5)	8/19(42.1)	23/39(59.0)
Liver transplant (among patients listed at any point)	29/35 (82.9)	46/74 (62.2)	19/24 (79.2)	40/59 (67.8)	19/24 (79.2)	39/57 (68.4)

Source: Reviewer's analysis, dataset: adsl, tte1 & agrp
Abbreviations: ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; HRS, hepatorenal syndrome; RRT, renal replacement therapy

Conclusion

The increased risk of serious respiratory failure is a significant safety concern. From a mechanistic standpoint, it is plausible that terlipressin could increase the risk of fluid overload and respiratory failure via effects on V1a or V2 receptors. Given the medical complexities and multiple potential causes of respiratory failure in these patients, however, it is challenging to determine how terlipressin may have contributed to serious respiratory failure events. The potential role of albumin use and fluid overload complicate the clinical presentation and management of these respiratory events.

The Applicant's risk mitigation plan was developed retrospectively, based on findings in the CONFIRM study, and it is unclear whether the proposed measures will adequately mitigate risk and/or whether the implementation of these measures could diminish efficacy. Specifically,

- Patients with HRS-1 have a high background rate of fluid overload, pneumonia, and dyspnea, which can be influenced by several pathologic factors. Thus any mitigation steps involving monitoring and/or managing these conditions without objective criteria and clear recommendations regarding dosing of terlipressin, diuretics or albumin will be difficult to implement. Thus, certain aspects of the proposed risk mitigation strategy introduce uncertainty and complexity regarding how to manage these patients. At the Terlipressin Advisory Committee Meeting, some committee members shared similar concerns that some factors of the mitigation plan may be difficult for clinicians to implement because of their subjective nature. The proposed mitigation strategy regarding management of fluid overload (reducing the administration of albumin and judicious use of diuretics) was actually implemented in CONFIRM (this was the only aspect of the plan used in CONFIRM). Despite these recommended instructions with respect to fluid

management, the incidence of fluid overload AEs was greater in the terlipressin arm than in the placebo arm (28% versus 16%, respectively).

- Post hoc, the Applicant has identified an ACLF score at which patients appear to be at higher risk of serious respiratory failure. Trial data (CONFIRM study and ISS) suggest that terlipressin-treated patients with advanced disease (e.g., ACLF Grade 3) are at higher risk of experiencing serious respiratory failure. Although it is plausible that patients with severe disease may have limited capacity to react or adjust to possible adverse effects of terlipressin on the respiratory system, it is not obvious how ACLF criteria involving assessments of bilirubin, international normalized ratio, or MAP directly relate to terlipressin's respiratory effects. Moreover, the Applicant is not proposing ACLF Grade 3 as a contraindication and currently describes the risk in Warnings and Precautions, which could result in uncertainty regarding to whom the terlipressin should be given.
- The proposed mitigation plan also recommends against use of terlipressin in patients with baseline SCr ≥5 mg/dL. The Applicant's analysis indicates that the probability of achieving verified HRS reversal decreases, regardless of treatment arm, as baseline SCr increases and suggests that the magnitude of the benefit (as assessed by terlipressin's effect on HRS reversal) decreases with increasing baseline SCr (see section 6.3.3). The risk of serious respiratory failure was observed in terlipressin-treated patients regardless of baseline SCr level. The Applicant clarified that the rationale for selecting this criterion is based on the likelihood of improving the overall benefit-risk profile of terlipressin rather than reducing the risk of respiratory failure events.

The Applicant evaluated the impact of the proposed risk mitigation on both safety and efficacy by excluding subjects with ACLF Grade 3 and SCr ≥ 5 mg/dL and removing an additional 11 subjects based on other components of the mitigation strategy. The impact of clinical mitigation on safety findings is likely overestimated given the uncertainty regarding the post hoc predictors (i.e., ACLF and SCr) and the overly optimistic outcomes when an additional 11 subjects are removed from the analyses based on clinical mitigation. The majority of 11 subjects were removed because it is thought that the mitigation guideline would have likely resulted in interruption of terlipressin because of the presence of conditions such as pneumonia or fluid overload during treatment. However, these serious respiratory failure events tended to occur soon after administration of terlipressin and there was no data supporting that the interruption of terlipressin would reverse or prevent serious respiratory failure events. There are also elements of the proposed plan that may be challenging to implement in typical patients with HRS. Thus the effects of these measures on both risk and benefit, without prospective testing, are uncertain.

In summary, it is rational to seek to identify an appropriate patient population to reduce the serious risk of respiratory failure and improve the overall outcomes. However, this exercise is particularly challenging considering the multifactorial causes of respiratory failure, the medical complexity of patients with HRS-1, and the limited size of the available database. Although excluding patients with ACLF Grade 3 could reduce the risk of serious respiratory failure to some degree, the effect of this post hoc predictor remains largely uncertain. Some of the proposed risk mitigation criteria are subjective (based on presence of respiratory symptoms, assessment and treatment of fluid overload) raising the possibility that terlipressin-related respiratory events might be challenging to identify and manage, a concern shared by some Advisory Committee members. Overall, the effectiveness of the proposed mitigation plan is difficult to estimate without additional clinical data to test it prospectively.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Based on population PK analysis using sparse PK data collected from REVERSE, combined with PK data from OT-0401, no significant effects of gender, age, creatinine clearance, Child-Pugh Score, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase , or total bilirubin were observed on terlipressin exposure. Clearance of terlipressin in patients with HRS-1 increases with higher body weight, whereas, body weight has no effect on the clearance or volume of distribution of lysine-vasopressin. Terlipressin is estimated to have approximately 1% of the V1 receptor activity of lysine-vasopressin. No dose adjustment based on intrinsic factors is needed.

Patients with HRS-1, by nature of their condition, have severe hepatic and renal impairment. Among all patients included in the population PK analysis, one had mild hepatic impairment, and another had mild renal impairment. All other patients had moderate/severe hepatic impairment, and moderate/severe renal impairment/end stage renal disease. The degree of hepatic or renal impairment does not have significant effect on the clearance of terlipressin or lysine-vasopressin. Based on data reported in healthy subjects, < 1% of terlipressin and < 0.1% of lysine-vasopressin is eliminated in urine. No dose adjustment is required in patients with renal impairment or hepatic impairment.

8.2. Drug Interactions

Terlipressin and lysine-vasopressin are metabolized by various tissue peptidases. In vitro study (RPT-STDY-0338) using human liver microsomes demonstrates that terlipressin is not a direct, time-dependent or metabolism-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 enzymes. It does not induce CYP1A2, CYP2B6 or CYP3A4 enzymes as measured by evaluating changes in mRNA expression in an in vitro study (RPT-STDY-0339). It is not an inhibitor or substrate of the human transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K. No clinical drug interactions are anticipated for terlipressin.

8.3. Pediatric Labeling / Plans for Pediatric Drug Development

The Applicant requested waiver of pediatric studies. Because terlipressin for the treatment of HRS-1 has an orphan drug designation, it is exempt from PREA requirements.

8.4. Pregnancy and Lactation

Discussion on labeling related to use of terlipressin in pregnant and lactating women will be deferred until the application is otherwise approvable. Upon resubmission, appropriate labeling

for use in these populations will be determined in collaboration with the Division of Pediatric and Maternal Health.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 22231 with respect to Chemistry, Manufacturing, and Controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators and CONFIRM appears to have been conducted in compliance with U.S. regulations pertaining to Good Clinical Practice. No clinical sites were inspected because review of financial disclosure information did not raise concern and efficacy findings were not driven by a single site.

11. Advisory Committee Summary

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 15, 2020 to discuss the new drug application for terlipressin for the treatment of hepatorenal syndrome type 1 (HRS-1).

Committee members generally agreed that the CONFIRM trial met its primary endpoint. There were, however, different views on whether terlipressin's effect on verified HRS reversal was accompanied by favorable trends in treatment effects on clinical outcomes. Most members noted a trend in improvement for renal replacement therapy-free survival, a clinically important outcome, in the terlipressin arm. Members noted that treatment effects on outcomes after liver transplant were challenging to interpret, mainly because the analyses were based on post-randomization variables. Members also thought that treatment effects on length of ICU stay were difficult to interpret for a variety of reasons. One member thought that the data supported efficacy in patients with alcoholic hepatitis at baseline, but questioned whether terlipressin provided benefit in patients without alcoholic hepatitis at baseline. Some also voiced concern that the proportion of patients on terlipressin who received liver transplants, the definitive therapy for HRS-1, was lower in the terlipressin arm than on placebo.

Committee members agreed that respiratory failure and fluid overload were serious risks associated with use of terlipressin and that a clear and effective risk mitigation strategy would be needed to ensure the product's benefits outweighed its risks. Some observed that the currently

proposed mitigation strategy included factors that might be difficult for hepatologists to implement because of their subjective nature (e.g., hepatologists may interpret the proposed instructions in different ways). Some voiced concern that the devised strategy was based on "slicing and dicing" the CONFIRM data and thought that the mitigation strategy should be prospectively tested and/or validated in a separate dataset.

When asked to vote on whether terlipressin should be approved for the treatment of HRS-1, eight Committee members voted "Yes" and seven members voted "No."

- In general, members who voted for approval cited the unmet need for treatments for HRS-1, a condition associated with a high mortality rate. Members further noted that there were no approved treatments for the condition and that there were more data on the efficacy and safety of terlipressin than for other therapies that are commonly used off-label to treat HRS-1. These members noted that CONFIRM met its primary endpoint of verified HRS reversal and that treatment with terlipressin was associated with favorable trends in renal replacement therapy-free survival. Some members noted the potential for terlipressin to be used as a "temporizing measure" to stabilize patients until liver transplant. There was general consensus that an adequate risk mitigation strategy would be needed. Proposals included a REMS (details not specified), patient consent (that patients would need to be educated on and understand risks), and/or a postmarketing study.
- Committee members who voted "No" voiced concern about safety and the ability of the proposed strategy to mitigate risk adequately because of difficulty with implementation and/or because the strategy had not been prospectively tested. These members did not believe that the benefits of terlipressin outweighed its risks. Some members also questioned the clinical significance of the efficacy findings.

III. Appendices

12. Summary of Regulatory History

The original IND was submitted on March 31, 2004. FDA granted Orphan Drug designation and Fast-Track designation on October 29, 2004 and April 15, 2005, respectively. The NDA was initially submitted on May 4, 2019, based on the findings in Study OT-0401. See Table 50 for an overview of key aspects of the regulatory history. See Table 4 for additional information on Studies OT-0401 and REVERSE.

Table 50. Summary of Key Regulatory History

Study	Key Regulatory History
OT-0401	5/4/2009: Initial NDA for terlipressin (022231) submitted • Primary endpoint (i.e., HRS reversal with treatment success at Day 14) did not reach statistical significance (p=0.13).
	11/4/2009: Complete Response Letter sent to Applicant stating: • OT-0401 showed modest reduction in SCr but failed to show durability of effect. • "Your most favorable analysis, using an endpoint developed post hoc with a generally unacceptable redefinition of treatment success, reaches statistical significance, but comes nowhere close to the p-value necessary to support approval based upon a single study." • "Need to conduct at least 1 additional adequate and well-controlled study... Study will need to be successful, using prespecified endpoint(s) and analytic plan, at p<0.05."
REVERSE	4/29/2015: Class 2 NDA resubmission • Primary endpoint (i.e., confirmed HRS reversal) did not reach statistical significance (p=0.22).
	5/22/2015: Incomplete response letter sent to Applicant stating: • "The REVERSE trial was not successful on its prespecified primary endpoint…a result that plainly does not meet the requirement stipulated in 4 Nov 2009 action letter."
CONFIRM	11/30/2015: Request for SPA by Applicant • Proposed primary endpoint: HRS reversal (the percentage of subjects with one serum creatinine value of ≤1.5 mg/dL by Day 14 or discharge).
	1/14/2016: SPA No-Agreement Letter sent to Applicant stating: • "The proposed primary endpoint is HRS reversal... A repeat serum creatinine measurement is needed to confirm that the initial value is not spurious." • To "qualify as having a primary endpoint event, subjects must not require renal replacement therapy within some reasonable time frame of the confirmed serum creatinine ≤1.5 mg/dL (say, within 14 days)." • We "expect to see favorable trends in clinical outcomes thought to be predicted by your surrogate."
	Additional communication from FDA to Applicant regarding primary endpoint: • Add the phrase, "Subjects must be alive without RRT for at least 10 days after achieving verified HRS reversal to qualify as having a primary endpoint event." • Define "on treatment" as up to 24 hours after the last dose of study drug.

Study	Key Regulatory History
	4/20/2016: SPA Agreement Letter sent to Applicant stating: • Agreed upon primary endpoint: Incidence of verified HRS reversal, defined as the percentage of subjects with two consecutive SCr values ≤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. • "For the purpose of approval, the data overall will need to establish a benefit that outweighs the risks of your product."
	10/21/2019: Pre-NDA Meeting between Division and Applicant • The discussion focused on additional analyses that could be conducted to assess whether treatment effects on clinical outcomes thought to be predicted by the study's primary endpoint (a surrogate endpoint) were tracking with the primary endpoint.

Abbreviations: HRS, hepatorenal syndrome; SPA, statistical analysis plan; SCr, serum creatinine; RRT, renal replacement therapy; TIPS, transjugular intrahepatic portosystemic shunt; FDA, U.S. Food and Drug Administration; NDA, new drug application

13. Pharmacology Toxicology Assessments and Additional Information

N/A

13.1. Summary Review of Studies Submitted Under the IND

N/A

13.2. Individual Reviews of Studies Submitted to the NDA

N/A

14. Clinical Pharmacology Assessment: Additional Information

N/A

14.1. In Vitro Studies

N/A

14.2. In Vivo Studies

N/A

15. Trial Design: Additional Information and Assessment

15.1. Important Study Dates

The study was conducted between July 13, 2016 (first patient enrolled) and July 24, 2019 (last subject, last visit). The database soft lock for interim analysis occurred on April 16, 2018 after 50% of subjects completed treatment (by Day 14 or discharge). Enrollment continued during the interim analysis. The final database lock occurred on August 12, 2019.

15.2. Protocol Amendments

The clinical protocol was amended three times. An overview of each amendment can be seen in Table 51.

Table 51. Overview of Protocol Amendments

Amendment No. and Date	Summary of Significant Changes
Amendment 1 5/9/2016	• Changes were made to address FDA recommendations included in the SPA Agreement letter (4/21/2016): – Definitions of HRS reversal (i.e., the percentage of subjects with HRS reversal without RRT to Day 30) and RRT (i.e., any procedure to replace nonendocrine kidney function) were clarified – Primary efficacy analysis timing after the final dose of study drug was changed from 72 hours to 24 hours – Definition of HRS recurrence by Day 30 was further clarified – Sample size calculation was revised to account for verified HRS reversal (i.e., two SCr values instead of one SCr value) – Description of the secondary efficacy analyses were revised/clarified – Instructions regarding actions to be taken in the event of suspected cardiac or intestinal ischemia were provided
Amendment 2 12/16/2016	• Changes were made to address FDA comments and recommendations (letter dated 10/14/2016): – Schedule of assessments modified to include an abbreviated physical examination conducted every day during the 14-day active study period – For subjects receiving vasopressors at baseline, the qualifying SCr would be taken after a 24-hour vasopressor washout – The definition of HRS recurrence was further clarified (i.e., another episode of HRS type 1 (defined the same as study entry criteria) by Day 30)

Amendment No. and Date	Summary of Significant Changes
Amendment 3 9/26/2018	• Applicant submitted a request (6/20/2018) for written feedback on a proposal to modify the primary endpoint to include some SCr values obtained after open-label vasopressor use and stated the following: – "Our rationale for this proposal is that open-label vasopressors may be administered short term in uses not related to the patient's renal dysfunction and do not constitute clinically meaningful therapy for HRS type -1" (e.g., administration of single low dose dobutamine for cardiac stress testing as part of liver transplant evaluation) • The Division issued an Advice Letter (7/30/2018) and recommended that the Applicant request a teleconference to discuss potential paths forward (teleconference occurred on 9/13/2018). The key point from both is as follows: – The Division did not object to "changing the primary endpoint definition to specify that serum creatinine values obtained after midodrine administration can be included if (1) the subject enrolled in CONFIRM on or after 8/17/2018 (the date the current proposal was submitted to the Agency) and (2) midodrine was started on day 1 and was administered to the subject for less than 24 hours" • After the teleconference, the following statement was added to sections of the protocol that address primary and secondary efficacy endpoints: – "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 (b) (6). SCr values will also be included if obtained after the administration of a single dose of dobutamine" • Special Protocol Modification Agreement issued on 12/4/2018

Abbreviations: HRS, hepatorenal syndrome; RRT, renal replacement therapy; SCr, serum creatinine; FDA, U.S. Food and Drug Administration

15.3. Study Phases

Screening

The screening period occurred prior to enrollment and consisted of establishing the diagnosis of HRS-1 as per guidelines and standard medical practice and confirming the eligibility for study participation. Serum creatinine values during hospitalization and details of albumin fluid challenge administration and diuretic withdrawal were noted.

Pretreatment

During the pretreatment period, baseline assessments and prior medication information was collected. The qualifying SCr value (i.e., the SCr value at least 48 hours after both diuretic withdrawal and the beginning of the albumin fluid challenge) was drawn during the pretreatment period. The qualifying SCr could not be drawn more than 8 hours prior to the start of study drug. If there was a delay in randomization of more than 8 hours, then the qualifying SCr value had to be redrawn. For subjects receiving vasopressors at baseline, the qualifying SCr was to be taken after a 24-hour vasopressor washout (Protocol Amendment 2, December 16, 2018).

Treatment

The treatment period was defined as the active study period, which extended from the initiation of study treatment through discharge or a maximum of 14 days (or 15 days if HRS reversal occurred on Day 14). See section titled “Dosing” for information regarding the dosing schedule.

Follow-up

The follow-up period began after the end of the study treatment and concluded 90 days following the start of treatment. The Day 30 (±10 days) follow-up visit was to be conducted in-person. The Day 60 (±14 days) and Day 90 (±14 days) follow-up visits could be conducted via telephone to assess survival, RRT, TIPS, and liver transplant status.

15.4. Study Assessments

Collection of Primary Endpoint

SCr data for the primary endpoint was collected at least daily until discharge or Day 14. SCr values obtained after midodrine administration were included if midodrine was started on Day 1, was administered for no more than 24 hours, and the subject was enrolled on or after (b) (6) (Protocol Amendment 3, September 26, 2018; see Table 51 for details). SCr values were also included if obtained after the administration of a single dose of dobutamine (Protocol Amendment 3, September 26, 2018). Following HRS reversal (SCr ≤1.5 mg/dL), repeat values for SCr had to be obtained a minimum of 2 hours after the first SCr value.

Clinical sites captured and reported any TIPS, liver transplant, or vasopressor use in the appropriate case report form (CRF) pages. Subjects were contacted to determine the status of survival without RRT at 10 days after the second SCr value ≤1.5 mg/dL was obtained. Study sites documented at least three attempts to contact the subject or the subject’s caregiver by phone to obtain RRT and vital status information. This information could be verified from the subject’s electronic medical records. All information related to RRT and vital status at Day 10 was reported in the electronic data capture system and was source verified by the site monitor.

Adverse Events of Special Interest

In light of terlipressin’s established mechanism of action and pharmacodynamic effects (i.e., development of central or peripheral ischemia and pulmonary congestion), additional information was collected from study sites for subjects who reported AEs with the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms: abdominal pain, chest pain, or dyspnea/wheezing/bronchospasm/pulmonary edema. These AEs were considered to be adverse events of special interest. Sites were required to complete an additional adverse events of special interest CRF page and provide information on the characteristics of the event, as well as clinical laboratory and/or other investigations conducted in relation to the reported event.

15.5. Study Procedures

Randomization

Randomization was managed centrally using an interactive voice and web response system. The randomization codes were generated by an independent statistician and were not accessible to blinded personnel (unless required during a medical emergency) during the study period. Subjects were stratified by qualifying SCr (<3.4 mg/dL or ≥3.4 mg/dL) and pre-enrollment LVP (at least one single event of ≥4 L within 3 to 14 days prior to randomization).

Blinding

The study was double-blinded using matching 6-mL glass vials containing a homogenous lyophilized white to off-white solid. The terlipressin vials contained 1 mg active ingredient and 10 mg mannitol and the placebo vials contained 11 mg of mannitol without the active ingredient. Each investigational site received kits of blinded, labeled active and placebo vials each numbered with unique, randomized identification numbers.

Dosing

Dosing Regimen

The dosing regimen was the same as that used in the OT-0401 and REVERSE studies. The starting dose of investigational product was 1 mg administered intravenously every 6 hours. For subjects achieving <30% decrease in SCr by Day 4 (after a minimum of 10 doses), the dose was escalated to 2 mg every 6 hours. Treatment was continued until 24 hours after two consecutive SCr values ≤1.5 mg/dL had been obtained or up to a maximum of 14 days. For subjects whose SCr first reached 1.5 mg/dL on Day 14, treatment continued until Day 15.

Individual Subject Dose Modification or Interruption

The dose was not increased in subjects with coronary artery disease or in the setting of circulatory overload, pulmonary edema, or bronchospasm. If dosing was interrupted because of an adverse event (other than cardiac or mesenteric ischemia), study drug could be restarted at the same or lower dose as per protocol, at the discretion of the investigator.

Individual Subject Dose Stopping Criteria

Subjects had their treatment discontinued if one of the following occurred:

- SCr was at or above baseline value on Day 4 (after a minimum of 10 doses)
- The subject underwent RRT, liver transplant, TIPS, or vasopressor therapy
- The subject had an AE of cardiac ischemia or mesenteric ischemia (treatment permanently discontinued)

Compliance

Subjects were dosed with investigational product during inpatient hospitalization. The treatment, dosage, and time of administration for each dose of study drug was documented. A monitor

reviewed subject source documents and drug accountability records to assess treatment compliance on an ongoing basis during site visits.

Concomitant Medications

As per standard medical practice, concomitant use of a constant dose of albumin (20 g/day to 40 g/day) in both treatment arms was strongly recommended. Prohibited medications included: midodrine or other vasopressor drugs (e.g., vasopressin, dopamine, dobutamine, norepinephrine), prostaglandin analogs (e.g., misoprostol), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen, diclofenac), and octreotide. Use of diuretics was strongly discouraged unless medically required for fluid overload, and were to be documented if used.

Follow-Up

Attempts were made to collect follow-up data (including required laboratory tests, SAEs, and mortality assessments) for all randomized subjects, whether or not they received their assigned study treatment or altered or discontinued study drug prematurely, except for those subjects who specifically withdrew consent for release of such information. Sites were instructed to contact subjects or family members via telephone, mail, or both to obtain this information. Withdrawal of consent for follow-up was to be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment was to be distinguished from withdrawal of consent for follow-up contact and from withdrawal of consent for nonsubject contact follow-up (e.g., medical records checks).

Retreatment

If judged by the investigator to be potentially beneficial, subjects who demonstrated at least a partial response during the initial treatment course (≥30% reduction in SCr) who developed a recurrence of HRS-1 during the study or follow-up period (up to study Day 90) could be retreated with initially assigned blinded study drug for a maximum of 14 days (from the beginning of the retreatment) with treatment and study procedures being identical to the initial therapy. To qualify for retreatment, the subject must again have met the study inclusion/exclusion criteria. Subjects were not rerandomized or restratified for the retreatment cycle. The follow-up schedule was based upon the original randomization.

15.6. Identification of Endpoints

Primary Endpoint

Primary endpoint events were identified programmatically based on the aggregate of SCr laboratory data and information captured in the CRF. Clinical sites captured and reported any TIPS, liver transplant, or vasopressor use in the CRF. Subjects were contacted regarding Day 10 RRT and vital statuses, with the information recorded in the CRF, as described in Appendix III.15.4 of this document.

Secondary Endpoints

Assessment of Recurrence

HRS-1 recurrence was assessed by the investigator during the first 30 days after discharge or Day 14 based upon the criteria listed below and serious AE data collected up to Day 30:

- 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
- 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
- The subject had no sepsis or uncontrolled bacterial infection or shock. If there was documented or suspected infection, the subject has at least 2 days of anti-infective therapy
- The subject did not have current or recent (within 4 weeks) treatment with or exposure to nephrotoxic agents
- The subject had no superimposed acute liver injury
- Proteinuria was less than 500 mg/day; the subject did not have evidence of obstructive uropathy or parenchymal renal disease on ultrasound or other imaging; or the subject did 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

All rehospitalizations after initial hospital discharge (except for planned hospital admissions or procedures) required an investigator assessment and opinion regarding possible recurrence of HRS-1. All available relevant medical records, MedWatch forms, discharge summaries, or other relevant source documents were to be requested and reviewed for all SAEs, including hospitalizations, until 30 days after discontinuation of study drug. If the investigator could not exclude a recurrence of HRS-1, the subject was considered to have a recurrence for the purposes of sensitivity analysis (Protocol Amendment 2, December 16, 2018).

Other Secondary Endpoints

HRS reversal was a programmed variable based on SCr values and dates/times of SCr, RRT, TIPS, liver transplant, and open-label vasopressor use. If the subject received treatment, and achieved one SCr value ≤1.5 mg/dL by Day 14 or discharge, while on treatment (up to 24 hours after the final dose of drug), and that SCr value occurred prior to RRT, TIPS, liver transplant, and/or open-label vasopressor use, then the subject was considered to have had HRS reversal.

Durability of HRS reversal was determined in the subjects with HRS reversal (identified as described for the primary endpoint above) based on evaluation of all RRT data up to Day 30 (i.e., if a subject did not have RRT on or before Day 30, then the subject met the criteria for durability of HRS reversal). The clinical sites tracked all patients through the follow-up period and recorded the date of initiation of RRT on the appropriate CRF pages, when applicable. The study sites documented at least three attempts to contact the subject or the subject's caregiver by phone to obtain information on RRT status. This information could be verified from the subject's electronic medical records. All information was reported in the electronic data capture system and was source verified by the site monitor.

15.7. Eligibility Criteria

Key Inclusion Criteria

2. At least 18 years of age
3. Cirrhosis and ascites
4. Rapidly progressive worsening in renal function to a SCr ≥2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks
5. No sustained improvement in renal function (<20% decrease in SCr and SCr ≥2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin

Key Exclusion Criteria

1. Serum creatinine level >7.0 mg/dL
2. At least one event of LVP ≥4 L within 2 days of randomization
3. Sepsis and/or uncontrolled bacterial infection (e.g., persisting bacteremia, persisting ascitic fluid leukocytosis, fever, increasing leukocytosis 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
7. Estimated life expectancy of less than 3 days
8. Superimposed acute liver injury due to drugs (e.g., acetaminophen), dietary supplements, herbal preparations, viral hepatitis, or toxins (e.g., Amanita toxin with mushroom poisoning, carbon tetrachloride), with the exception of acute alcoholic hepatitis
9. Proteinuria >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 (>50 red blood cells per high power field in the absence of recent catheterization) on urinalysis
12. Subjects known to be pregnant
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. Use of vasopressors (e.g., norepinephrine, epinephrine or vasopressin, dopamine, or other vasopressors) of ≥3 consecutive days within prior 14-day screening period. Patients receiving a vasopressor other than midodrine within 24 hours of qualifying SCr are excluded, i.e., a 24-hour washout is required prior to enrollment (Note: Patients receiving midodrine and octreotide could be enrolled; midodrine and octreotide treatment must be stopped prior to randomization)

16. Efficacy: Additional Information and Assessment

Calculation of Primary Endpoint

The Z score is based on the difference in proportions of subjects with verified HRS reversal. By working backwards, the FDA statistician was able to derive that the Z score is equal to $\frac{\hat{p}_1-\hat{p}_0}{\sqrt{\hat{p}_{pool}(1-\hat{p}_{pool})\left\{\frac{1}{n_0}+\frac{1}{n_1}\right\}}}$ where $n_0 = 101$, $n_1 = 199$, $\hat{p}_0 = \frac{16}{101}$, $\hat{p}_1 = \frac{58}{199}$, and $\hat{p}_{pool} = \frac{58+16}{199+101}$.

There are no concerns with using this statistic for the primary analysis, but it would have been better to have it clearly specified in the statistical analysis plan and protocol so that there would be no confusion later. It could have been defined mathematically or descriptively.

Durability of Treatment Effect in Patients Who Did Not Receive a Liver Transplant

Of the 44 subjects on terlipressin who met the primary endpoint of verified HRS reversal and did not receive a liver transplant, eight subjects (18%) either met the prespecified criteria for HRS recurrence by Day 30 or HRS recurrence could not be excluded in those subjects. None of the 11 placebo arm subjects met criteria for HRS recurrence by Day 30 (see Table 52).

Table 52. HRS Recurrence in Subjects With Verified HRS Reversal in Subpopulation of Subjects Who Did Not Receive a Liver Transplant

n (%)	Terlipressin N=44	Placebo N=11
HRS recurrence by Day 30 (or could not exclude HRS recurrence)	8 (18)	0 (0)

Source: FDA analysis
Abbreviation: HRS, hepatorenal syndrome

Additional Analyses in Subgroups of Patients with and without Alcoholic Hepatitis at Baseline

Exploratory analyses were conducted to determine the proportion of subjects in each arm who died or initiated RRT based on alcoholic hepatitis status at baseline. As seen in the table below, the results in the subgroups were largely consistent with the findings for HRS reversal.

Table 53. Summary of Initiation of RRT and/or Death to Day 90 in Subgroups of Patients With and Without Alcoholic Hepatitis at Baseline, ITT Population

	Terlipressin	Control
Alcoholic hepatitis present at baseline	N=81	N=39
RRT-free survival	27 (33%)	9 (23%)
RRT initiation or death	54 (67%)	30 (77%)
RRT initiation	19 (23%)	11 (28%)
Death without preceding RRT	35 (43%)	19 (49%)
Death with or without preceding RRT	43 (53%)	21 (54%)
Alcoholic hepatitis not present at baseline	N=118	N=62
RRT-free survival	40 (34%)	19 (31%)
RRT initiation or death	78 (66%)	43 (69%)
RRT initiation	39 (33%)	28 (45%)
Death without preceding RRT	39 (33%)	15 (24%)
Death with or without preceding RRT	57 (48%)	24 (39%)

Source: FDA analysis
Abbreviations: RRT, renal replacement therapy; ITT, intent-to-treat

RRT-Free Survival in Subgroup of Patients Who Did Not Receive A Liver Transplant

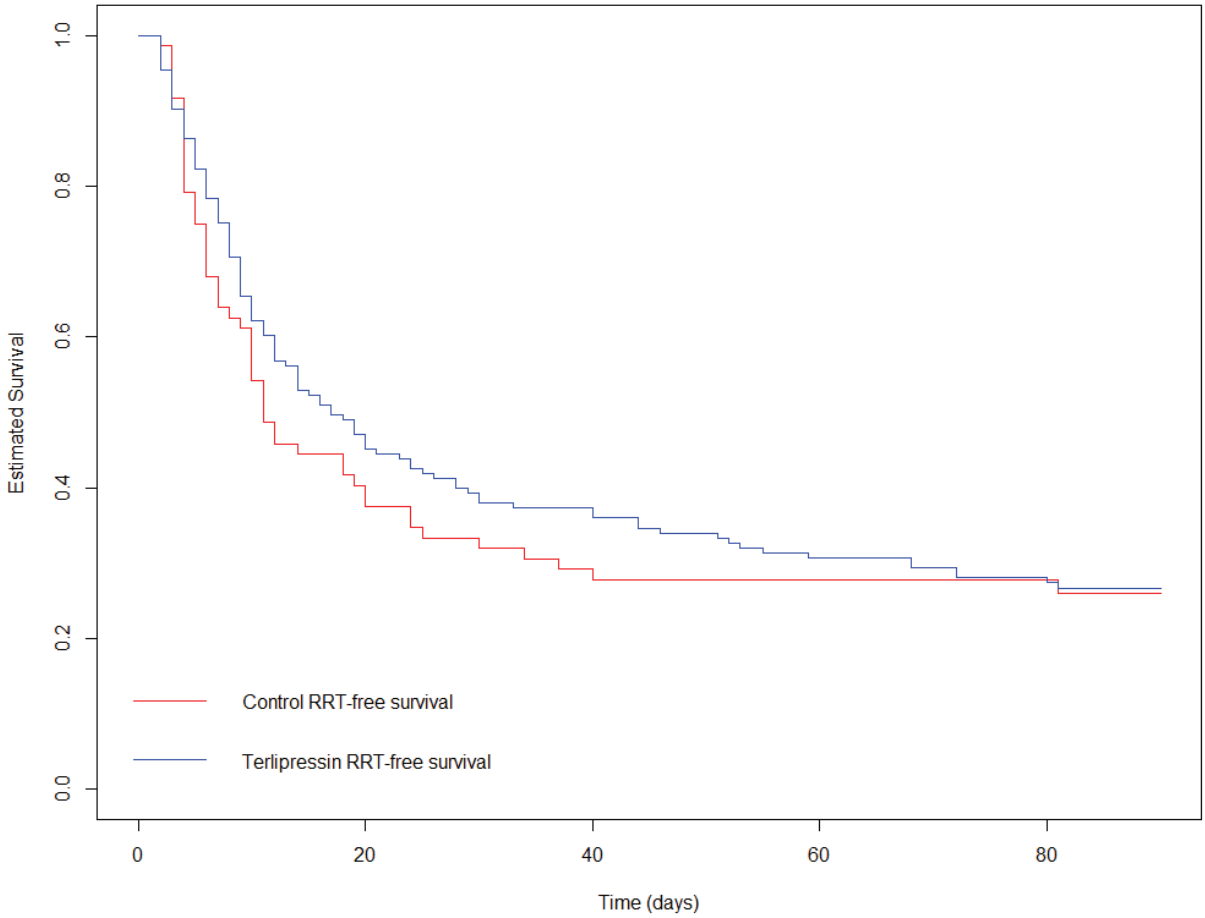
RRT-free survival was evaluated in the subgroup of subjects who did not receive a liver transplant. The results of these analyses can be found in the table and K-M curves below. As seen in the table and figure, the majority of subjects who did not receive a transplant either initiated RRT or died by Day 90, with no difference between treatment (73% terlipressin versus 74% placebo).

Table 54. Summary of Initiation of RRT and/or Death to Day 90 by Treatment Arm in Subjects Who Did Not Receive Liver Transplant, ITT Population

Event	Terlipressin (N=153)	Placebo (N=72)
RRT or death	112 (73%)	53 (74%)
RRT	38 (25%)	19 (26%)
Death without RRT	74 (48%)	34 (47%)
Death with or without RRT	103 (67%)	45 (63%)

Source: FDA analysis, dataset tte1
Abbreviations: RRT, renal replacement therapy; ITT, intent-to-treat

Figure 11. RRT-Free Survival Over Time to Day 90 by Treatment Arm in Subjects Who Did Not Receive Liver Transplant, ITT Population



Source: FDA analysis
Abbreviations: RRT, renal replacement therapy; ITT, intent-to-treat

Renal Replacement Therapy Status Before and After Receiving a Liver Transplant

As seen in the table below, of the patients who received a liver transplant, 35% of patients on terlipressin and 62% of patients on placebo were receiving RRT prior to their transplant, with the most common reason recorded as “fluid overload.” The mean number of days on RRT prior to liver transplant was similar between the two groups (12.4 (SD 17.4) days terlipressin versus 12.9 (SD 13.2) days placebo). Of these patients, 69% on terlipressin and 39% on placebo did not require RRT after their transplant. There were similar proportions of patients in each arm who were not on RRT prior to their transplant and did not require RRT after their transplant (87% on

terlipressin versus 82% on placebo). We find these analyses difficult to interpret, mainly because they are based on a post-randomization variable.

Table 55. Summary of RRT Status Pre- and Post-Liver Transplant, ITT Population

Event	Terlipressin (N=46)	Control (N=29)
On RRT pre-transplant	16 (35%)	18 (62%)
On RRT post-transplant	5/16 (31%)	11/18 (61%)
Not on RRT post-transplant	11/16 (69%)	7/18 (39%)
Not on RRT pre-transplant	30 (65%)	11 (38%)
On RRT post-transplant	4/30 (13%)	2/11 (18%)
Not on RRT post-transplant	26/30 (87%)	9/11 (82%)

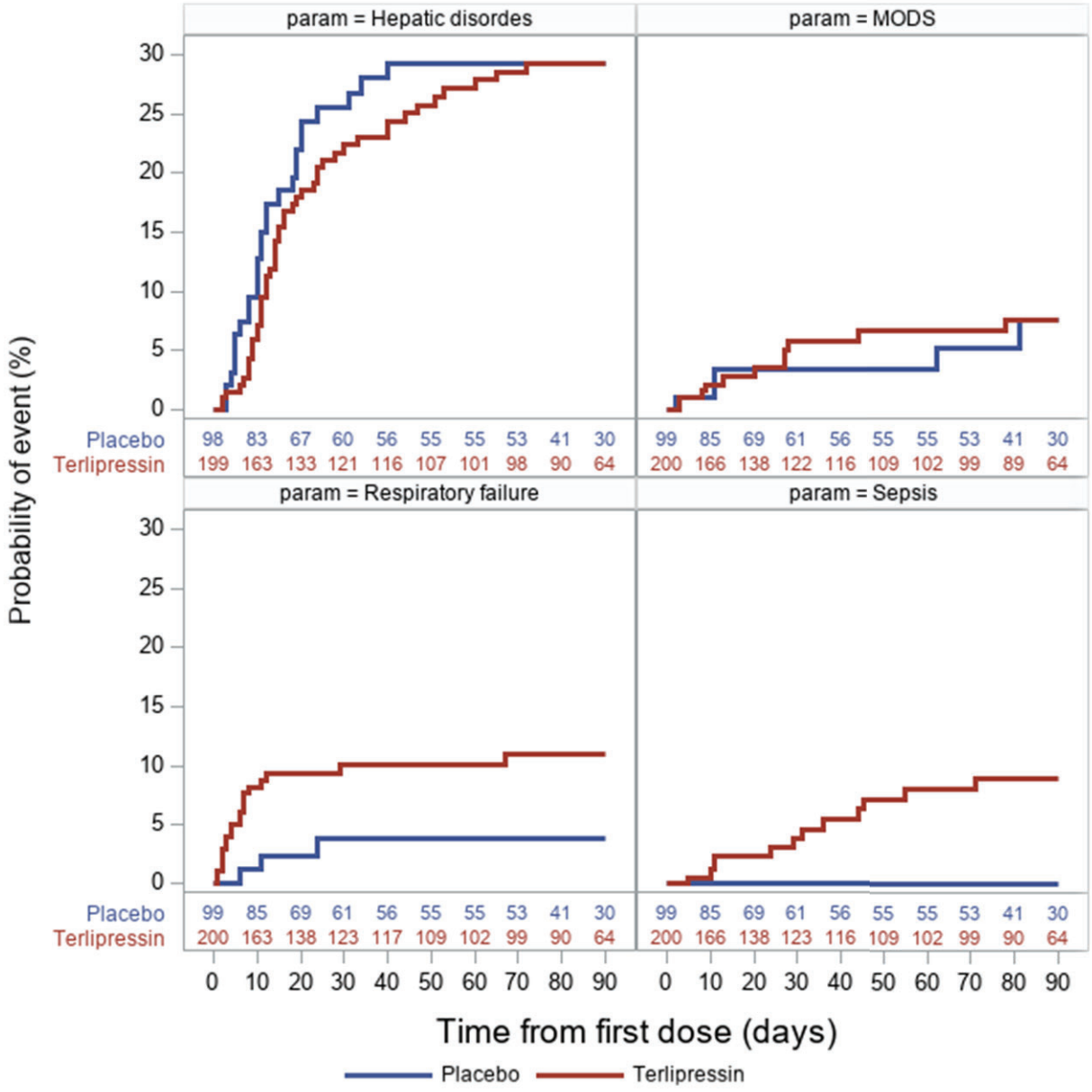
Source: FDA analysis, dataset tprrt
Abbreviations: RRT, renal replacement therapy; ITT, intent-to-treat

17. Clinical Safety: Additional Information and Assessment

17.1. Timing of Death by AE Categories of Interest

The figure below shows the K-M estimates of deaths by AE categories of interest, which provide some insights on the differences observed in overall mortality. For fatal events caused by hepatic disorders (upper left plot), there was an early separation between the arms favoring terlipressin. The curves further separated after Day 20 and through Day 40; however, the difference gradually decreased with more hepatic fatal events occurring in the terlipressin arm after Day 40. For respiratory failure (lower left), an early separation was observed for fatal events with the majority of deaths in the terlipressin arm (>80%) occurring within 10 days of treatment initiation (median onset: 5 days). Fatal events due to MODS (upper right) and sepsis (lower right) were more evenly distributed in the terlipressin arm over time (median onset was 20 and 30 days, respectively). Overall, compared to the placebo arm, there was a higher incidence of fatal respiratory events in the terlipressin arm early in the trial followed by a slightly higher incidence of deaths due to hepatic disorders and sepsis/septic shock.

Figure 12. Kaplan-Meier Estimates of Death b_ AE Cate_or_, Safety Population, CONFIRM



Source: Reviewer's analysis ISS data: adsl & adae
Sepsis AEs include sepsis, septic shock and sepsis syndrome
Abbreviations: MODS: multiple organ dysfunction syndrome

17.2. Narratives Review of Respiratory Failure

Brief summaries of the narratives for the 28 subjects on terlipressin in the CONFIRM study with the SAE of respiratory failure are listed below.

Subject 1

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 10 and MELD score of 40 at baseline and was admitted to the hospital for alcoholic hepatitis. Prior to the first dose of terlipressin on Day 1, the subject had received a total of 300 gm of albumin over 2 days of his hospitalization. (b) (6) also had a transjugular liver biopsy 6 hours prior to his initial dose of terlipressin and received 6 liters (L) of oxygen after his biopsy. His post-biopsy arterial blood gas results were considered within normal limits on Day 1. (b) (6) received a total of 200 gm of albumin on Day 1. The subject received his initial dose of terlipressin (1 mg IV) at (b) (6) on Day 1. His oxygen saturation worsened overnight and the subject developed severe acute respiratory failure on Day 2 at (b) (6). (b) (6) was placed on BiPAP and moved to the ICU. The subject's condition continued to worsen despite an administration of 120 mg IV furosemide and (b) (6) died the morning of Day 2 due to respiratory failure; an autopsy was not performed. The subject received a total of three doses of terlipressin (each 1 mg), with the last dose of terlipressin administered 2 hours before (b) (6) death.

Subject 2

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 10 at baseline and was admitted for vertebral osteomyelitis (MELD score not reported). The subject experienced acute dyspnoea on Day 2 of terlipressin initiation and was diagnosed with severe acute respiratory distress syndrome (ARDS). His electrocardiogram (ECG) revealed no clinically significant findings. (b) (6) chest x-ray revealed bilateral perihilar opacities and a small right pleural effusion. The subject's terlipressin was discontinued on Day 3 due to the initiation of RRT for fluid overload. He had received a total of nine doses of terlipressin (each 1 mg IV). The subject had been receiving 100-200 gm/day of albumin prior to the initiation of RRT. The event of ARDS was considered resolved on Day 11. The subject remained on RRT until a liver and kidney transplant was completed on Day 60.

Subject 3

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 10 and MELD score of 38 at baseline and was admitted for hepatic encephalopathy and upper gastrointestinal bleeding requiring intubation for airway protection (4 days prior to terlipressin initiation). The subject was extubated 2 days prior to terlipressin administration after an esophagogastroduodenoscopy was performed. The subject was started on albumin (total 200 gm), midodrine, and octreotide after extubation. One day prior to terlipressin administration, the subject's oxygen requirement started to increase and he was started on high flow nasal cannula oxygen. The subject experienced severe respiratory failure 2 hours after the first dose of terlipressin (1 mg IV) on Day 1 and terlipressin was permanently discontinued. A chest x-ray revealed worsening pulmonary edema with bilateral pleural effusions. The subject's oxygen saturation declined and he was transitioned to comfort care per the family's request. (b) (6) died in the morning on Day 2. An autopsy was not performed.

Subject 4

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 9 and MELD score of 26 at baseline and was admitted for acute kidney injury. The subject had a gradual onset of mild abdominal pain 2 days after terlipressin initiation (Day 2), which resolved after administration of tramadol and a paracentesis (4 L of fluid removed) on Day 3. The subject had been receiving 100-125 gm/day of albumin. After the paracentesis on Day 3, the subject experienced hypoxia, first requiring oxygen via nasal cannula and later progressing to noninvasive ventilation (not otherwise specified). The subject was transferred to the ICU on Day 4, and required BiPAP support. Chest x-ray revealed pulmonary edema. (b) (6) developed severe respiratory failure unresponsive to aggressive diuresis. Terlipressin was stopped on Day 4 as the subject's creatinine (3.3 mg/dL) was above baseline (3.0 mg/dL) (protocol specification). (b) (6) had received a total of 10 doses of terlipressin (each 1 mg IV). Paracentesis was performed on Day 5 (2.3 L removed) and the acute respiratory failure resolved on Day 7. The subject received a transplant on Day 13 and underwent hemodialysis on Day 15 (reason not specified).

Subject 5

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 10 and MELD score of 29 at baseline and was admitted for cirrhosis and transplant evaluation. The subject had trouble breathing 3 days after initiation of terlipressin (Day 3). (b) (6) had been receiving 25-100 gm/albumin per day since hospital admission. On Day 4, a chest x-ray revealed pulmonary edema and increased patchy opacities in both lungs. The subject developed leukocytosis and was diagnosed with severe multifocal pneumonia and severe ARDS the same day. The subject experienced severe acute respiratory failure and was started on BiPAP. A few hours later, (b) (6) was transferred to the ICU, intubated, and started on antibiotics. On Day 6, terlipressin was discontinued due to HRS reversal (SCr) 1.4 and 1.5 mg/dl) on Day 5 (protocol specification). Furosemide was administered for fluid overload on Day 6 and two paracentesis procedures were performed on Day 7 and Day 9 with administration of albumin. On Day 11, the events of acute respiratory failure and ARDS were reported as resolved, while the events of pneumonia and pulmonary edema were reported as resolving. On Day 16. the subject experienced worsening respiratory distress with severe hypercarbic respiratory failure and was intubated. The subject was suspected of having developed severe sepsis (source unknown). The events of respiratory failure and sepsis were resolved 3 days later. The subject died on Day 30, with the reason reported as severe hepatic failure.

Subject 6

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 11 and MELD score of 40 at baseline and was admitted to the hospital with decompensated liver cirrhosis and acute renal failure. The subject developed cardiac arrest with pulseless electrical activity secondary to severe respiratory failure and hypoxia in the setting of severe aspiration on Day 5. On Day 6, the subject was started on RRT and terlipressin was permanently discontinued (protocol specification). On Day 8, the subject developed multiple organ dysfunction syndrome and died. The subject had been receiving 12.5-62.5 gm/day of albumin during (b) (6) hospitalization.

Subject 7

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 13 and MELD score of 40 at baseline and was admitted to the hospital for management of liver and renal failure. Three days after initiation of terlipressin (Day 3), the subject experienced aspiration pneumonia which led to severe respiratory failure and intubation. The subject had received a total of seven doses of terlipressin (each 1 mg). (b) (6) dose of study medication was increased to 2 mg IV every 6 hours on Day 4 (per protocol). He had been receiving 25-75 gm/day of albumin until Day 6. The subject developed moderate pyrexia on Day 6 and a moderate seizure on Day 9. Both events were considered as "nonserious" by the investigator. No action was taken with the study medication subsequent to those events. Treatment with terlipressin was completed due to verified HRS reversal on Day 12 (SCr 1.4 and 1.3 mg/dL). On Day 13, the event of respiratory failure was considered resolved after 10 days.

Subject 8

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 12 and MELD score of 35 and was admitted to the hospital for spontaneous bacterial peritonitis. Prior to receiving the first dose of terlipressin on Day 1, the subject had an oxygen saturation of 94%. The subject had moderate coffee ground emesis in the evening after the first dose of terlipressin. (b) (6) subsequently received two more doses of terlipressin on Day 1 (each 1 mg). The subject had been receiving 25-100 gm/day albumin since hospital admission 10 days prior to terlipressin initiation. In the early morning on Day 2, the subject developed moderate respiratory failure with an oxygen saturation ranging from 60% to 70%, decreased blood pressure (85/55 mm Hg) and a decreased level of consciousness. The subject was intubated and transferred to the ICU by noon and a chest x-ray revealed increasing congestive heart failure and increasing opacification of the lower right lung, suspicious for pneumonia and/or aspiration; however, a firm diagnosis was not made. Treatment with terlipressin was discontinued due to the event of respiratory failure. All medical care was withdrawn on Day 3 per the subject's wishes. The subject died on Day 4.

Subject 9

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 9 and MELD score of 37 at baseline and was admitted to the hospital for acute alcoholic cirrhosis, alcoholic hepatitis, and renal insufficiency. The subject had normal oxygen saturation at baseline (99%). The subject received the first dose of terlipressin in the evening on Day 1 and had decreased oxygen saturation (93%) on Day 2. A chest x-ray revealed bilateral consolidation at the lung bases. The subject was treated with supplemental oxygen and antibiotics. Despite treatment, the subject's oxygen saturation continued to decrease to 60% in the evening of Day 2. (b) (6) was diagnosed with respiratory failure due to aspiration pneumonia, transferred to the ICU and intubated. Terlipressin was discontinued on Day 4 due to the serious event of circulatory collapse (blood pressure (BP) 70/40 mm Hg). Vasopressors were initiated. The subject remained on mechanical ventilation in the ICU. The subject had been receiving 25-50 gm/day albumin. On Day 14, the subject was extubated, and the event of respiratory failure was considered resolved. On Day 29, the subject experienced severe aspiration pneumonia and sepsis resulting in death. Blood culture was positive for vancomycin resistant enterococcus faecium.

Subject 10

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 10 and MELD score of 40 at baseline and was admitted to the hospital for a hepatitis B flare-up leading to acute on chronic liver failure. The subject's terlipressin dose was discontinued on Day 5 due to his SCr (3.5 mg/dL) being higher than baseline (3.1 mg/dL) (per protocol). On Day 8, the subject experienced severe respiratory failure and a chest x-ray revealed bilateral airspace opacities and pleural effusions. The subject had been receiving 25-50 gm/day of albumin. The subject was transferred to the ICU and intubated. Dialysis was initiated on the same day. The subject died on Day 9, with the reason reported as respiratory failure. An autopsy was not performed.

Subject 11

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 11 and MELD score of 40 at baseline and was admitted to the hospital due to decreased level of consciousness. Prior to the first dose of terlipressin, the subject's vital signs were as follows: oxygen saturation 98%, BP 104/60 mm Hg, and HR 79 bpm. Terlipressin was discontinued on Day 5 due to HRS reversal (SCr 0.8 and 0.9 mg/dL) (total 16 doses administered, each 1 mg). Also, on Day 5, the subject was found to have elevated BP (165/59 mm Hg) and HR (105 bpm). On Day 6, the subject developed severe respiratory failure and was transferred to the ICU and intubated. The subject had been receiving 25-100 gm/day of albumin up until that point. Also, on Day 6, the subject underwent paracentesis (3.9 L removed). (b) (6) systolic BP (141 mm Hg) and HR (110 bpm) remained high. A subsequent chest x-ray revealed a possible diagnosis of atelectasis and a persistent minor opacity in the bottom of right lung. Subsequent paracentesis procedures were performed on Days 8, 9, and 11, with a total of 10.1 L of fluid removed. An ECG on Day 9 was unremarkable. On Day 12, a chest x-ray revealed findings that were questionable for pneumonia and/or aspiration. The subject died on Day 14, with the reason reported as respiratory failure.

Subject 12

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 9 and MELD score of 39 at baseline and was admitted to the hospital due to decompensated liver cirrhosis and acute kidney injury. A chest x-ray performed 3 days after initiation of terlipressin (Day 3) revealed left bibasilar consolidation and/or atelectasis and small bilateral pleural effusions. Terlipressin was discontinued per protocol on Day 5 after 17 total doses (all 1 mg IV) due to increased SCr (3.51 mg/dL) compared to baseline (2.7 mg/dL). On the same day, the subject had increasing abdominal distension and mild shortness of breath. The subject had been receiving 25-75 mg/day of albumin. On the evening of Day 5, the subject was diagnosed with moderate pulmonary edema. (b) (6) developed acute respiratory failure with hypoxia, requiring intubation and mechanical ventilation. RRT was initiated for anuric acute kidney injury and metabolic acidosis. On Day 6, the subject developed worsening mental status thought to be due to hepatic encephalopathy. A chest x-ray revealed possible worsening pulmonary edema. In the morning of Day 7, the subject developed severe respiratory failure and metabolic encephalopathy. The subjects died from hypoxic respiratory failure in the afternoon of Day 7. An autopsy was not performed.

Subject 13

This (b) (6)-year-old (b) (6) had a Child Pugh score of 11 and MELD score of 30 at baseline and was admitted to the hospital for treatment of possible HRS. The subject had an endoscopic retrograde cholangiopancreatography on the first day of terlipressin administration (Day 1). Following the procedure on Day 2, the subject had a severe anesthetic complication with coma, requiring ICU transfer and intubation. Per protocol, terlipressin was discontinued on Day 4 due to the initiation of dialysis for volume overload. On Day 6, the subject was extubated. The subject had been receiving 25-50 gm/day of albumin. On Day 11, the subject underwent surgery to perform a liver transplant; however, the transplantation was unable to occur due to the presence of abdominal adhesions. On the same day, the subject developed severe acute respiratory failure requiring transfer to the ICU and intubation again. The subject died the next day with the reason reported as acute respiratory failure.

Subject 14

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 11 and MELD score of 37 at baseline and was admitted to the hospital for evaluation of abnormal laboratory values. Terlipressin was discontinued on Day 6 after 19 doses were administered (all 1 mg IV) due to verified HRS reversal (SCr 1.5 and 1.2 mg/Dl). On Day 7, the subject underwent large volume paracentesis (4 L fluid removed) followed by administration of 50 gm albumin. On Day 8, the subject experienced severe hypotension, severe respiratory failure, and severe atrial fibrillation requiring transfer to the ICU and intubation. Sepsis was suspected, but not confirmed (cultures negative). On Day 10, the subject died with the reason reported as severe septic shock.

Subject 15

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 12 and MELD score of 40 and was admitted to the hospital for worsening liver and renal function and altered mental status. The subject experienced mild dyspnea and mild wheezing on Day 2, which resolved on Day 3 after the administration of salbutamol. The 3 days prior to terlipressin initiation, the subject had been receiving 100-125 gm/day of albumin and continued to receive albumin 25 gm/day once terlipressin was initiated. On Day 4, he received albumin, bumetanide, and furosemide for hypervolemia and fluid overload. No paracentesis was performed. Per protocol, the subject's terlipressin was discontinued on Day 5 due to SCr (3.1 mg/Dl) being above baseline (2.7 mg/Dl). Later on Day 5, the subject was unresponsive and was thought to have had respiratory failure secondary to aspiration. He was intubated and transferred to the ICU. A bronchoscopy revealed positive results for vancomycin-resistant enterococci. On Day 8, (b) (6) was started on RRT (reason not known). On Day 16, the event of respiratory failure was considered resolved, but the subject remained hospitalized. The subject died on Day 31 with the reason reported as recurrence of sever septic shock.

Subject 16

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 14 and MELD score of 40 at baseline and was admitted to the hospital due to spontaneous bacterial peritonitis and pre-transplant evaluation. Baseline chest x-ray revealed a small bilateral pleural effusion. On Day 5, the subject was found to have cryptococcal meningitis based on a positive lumbar puncture, which was treated with cefuroxime and fluconazole. On the same day, the subject developed shortness of

breath with activity and supplemental oxygen was initiated. A chest x-ray revealed new bilateral infiltrates, most likely pneumonia. He had been receiving 25-150 gm/day of albumin. Per protocol, terlipressin was discontinued on Day 7 due to verified HRS reversal (2 SCr 1.5 mg/Dl). Later that day, the subject went into severe respiratory failure, was intubated, and transferred to the ICU. A subsequent bronchoscopy revealed aspiration pneumonia. On Day 12, the respiratory failure was considered resolved and the subject was extubated. Also, on Day 12, he was started on RRT for uremia. The subject died on Day 41 with the reason reported as sepsis.

Subject 17

This (b) (6)-year-old (b) (6) had a Child Pugh score of 13 and MELD score of 40 at baseline and was admitted to the hospital for gastrointestinal bleeding. During his hospitalization, he had been receiving 50-200 gm/day of albumin. On Day 6, the subject started to experience respiratory distress, which led to severe acute hypoxic respiratory failure requiring intubation and ICU transfer a few hours later. A chest x-ray showed increased bilateral infiltrates thought to be due to volume overload and/or aspiration. The subject subsequently developed severe vasodilatory shock thought to be due to sepsis from aspiration pneumonia. On Day 7, terlipressin was permanently discontinued due to the vasodilatory shock. (b) (6) was transitioned to comfort care and died later on Day 7.

Subject 18

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 9 and MELD score of 30 at baseline and was admitted to the hospital with hepatic encephalopathy. The subject's baseline vital signs included 92% oxygen saturation and respiratory rate of 26 bpm. On Day 1, following initiation of terlipressin, the subject experienced abdominal pain, diarrhea and vomiting. On Day 2, she developed mild tachypnea. On Day 3, (b) (6) had severe hemorrhagic diarrhea and severe hematemesis that was considered life-threatening by the investigator, as well as worsening encephalopathy. On Day 4, the subject developed severe respiratory failure and mild atrial fibrillation with rapid ventricular response that required increased oxygen. (b) (6) was started on BiPAP and administered furosemide. Chest x-ray revealed bilateral multilobar lung consolidation. Study treatment was permanently stopped due to respiratory failure (Day 4). Bilateral multilobar lung consolidation was revealed in an x-ray. Per family's request, (b) (6) was transitioned to comfort measures only. On Day 4, the subject died with the reason reported as respiratory failure.

Subject 19

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 11 and MELD score of 32 at baseline and was admitted to the hospital with nonalcoholic steatohepatitis and acute kidney injury. After 4 days of treatment with terlipressin (Day 4), the subject experienced mild rapid breathing (respiratory rate 18 bpm). Chest x-ray revealed a patchy ill-defined opacifications of the left perihilar region and right lower lobe. On the same day, the subject had a nonserious event of fluid overload and was started on furosemide. On Day 5, the fluid overload event was report as resolved. On Day 13, the subject experienced severe respiratory failure (oxygen saturation 91%), which was treated with furosemide. On Day 14, terlipressin was discontinued following verified HRS reversal (SCr 1.3 mg/Dl). On Day 15, (b) (6) was discharged from the hospital. The subject underwent two large volume paracenteses, one on Day 27 (6 L removed) and another on Day 35

(6 L). On Day 41, (b) (6) was re-admitted to the hospital with severe cardiac failure. On Day 46, the event of cardiac failure was considered resolved after two paracenteses, a Denver shut placement, and treatment with furosemide and spironolactone.

Subject 20

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 12 and MELD score of 40 at baseline and was admitted to the hospital for confusion and agitation. After 3 days of treatment with terlipressin (Day 3), the subject experienced severe pulmonary edema and moderate hypoxia. (b) (6) was transferred to the ICU, intubated, and started on high doses of diuretics. Chest x-ray revealed extensive bilateral pulmonary infiltrates. On Day 4, terlipressin was permanently discontinued due to the respiratory adverse events. Despite IV furosemide, vasopressin and norepinephrine, the subject continued to have hypotension and had an acute exacerbation of encephalopathy and jaundice. On Day 5, the subject's care was withdrawn, and (b) (6) died on Day 6.

Subject 21

This (b) (6)-yaer-old (b) (6) had a Child Pugh Score of 12 and the MELD score of 40 at baseline and was admitted to the hospital with confusion. Two days after initiation of terlipressin (Day 2), the subject had diffuse bilateral pulmonary edema, which was initially treated with bumetanide and BiPAP. On Day 3, the subject's developed respiratory failure requiring intubation. On Day 4, the subject experienced severe hypotensive shock due to a severe upper gastrointestinal (GI) bleed. On the same day, (b) (6) was transitioned to comfort care and terlipressin was permanently discontinued. On Day 4, the subject died.

Subject 22

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 13 and MELD score of 39 at baseline and was admitted to the hospital with renal failure. Four days before initiation of terlipressin (Day -4), the subject's chest x-ray revealed an airspace consolidation in the right lung, possibly due to pneumonia from aspiration of a hemorrhage (diagnosis was not firm). On Day 1 (initiation of terlipressin), the subject experienced acute hypoxic respiratory failure and was diagnosed with encephalopathy and right lower lobe pneumonia. On Day 2, the subject's experienced severe respiratory failure and was started on high flow oxygen at 60%. A second dose of terlipressin was administered 2 hours later. Five hours later, the subject was transitioned to comfort care. A few hours later on Day 2, the subject died. An autopsy was not performed.

Subject 23

This (b) (6)-year-old (b) (6) had a MELD score of 40 at baseline (Child Pugh Score not reported) and was admitted to the hospital with decompensated hepatic cirrhosis. Per protocol, (b) (6) terlipressin dose was increased from 1 mg every 6 hours to 2 mg every 6 hours on Day 4. On Day 7, the subject became encephalopathic and developed a severe respiratory tract infection leading to severe respiratory failure. Intubation was not preformed per subject's wishes. Terlipressin was permanently discontinued the same day due to respiratory failure. The subject died on Day 7.

Subject 24

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 8 and MELD score of 36 at baseline and was admitted to the hospital with hepatic encephalopathy. After the first dose of terlipressin, the subject experienced nonserious GI symptoms (nausea, vomiting, diarrhea) and the terlipressin dose was subsequently reduced from 1 mg to 0.5 mg every 6 hours. On Day 2, furosemide and albumin were initiated to treat a moderate pleural effusion. On Day 3, a paracentesis was performed and 3 L of fluid was removed. On Day 4, the terlipressin dose was then increased back to 1 mg every 6 hours. On Day 9, a chest x-ray revealed that the pleural effusion had worsened and the subject underwent thoracentesis the next day (Day 10). (b) (6) had received 50 gm of albumin on Day 9 and 100 gm of albumin on Day 10. Approximately 2 hours after the thoracentesis procedure, the subject experienced shortness of breath with oxygen saturation of 76% on 4 L/min of nasal cannula oxygen and she was started on BiPAP. The subject was later diagnosed with pneumonia of moderate severity. The serious event of respiratory failure was considered resolved on Day 11. Treatment with terlipressin was stopped on Day 14 following HRS reversal (2 SCr 1.4 mg/dL).

Subject 25

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 8 and MELD score of 16 at baseline and was admitted for orthostatic hypotension and TIPS occlusion. The subject developed severe respiratory failure with mild dyspnea and moderate chest pain 3 days after initiation of terlipressin (Day 3). The same day, paracentesis was performed (5 L of fluid removed) and the subject received 75 g albumin. On Day 4, the subject's renal function continued to decline and the he was administered diuretics. The next few days, the subject had ongoing issues with hypoxemic respiratory failure and tachypnea, thought to be due to volume overload. On Day 7, the subject underwent another paracentesis (3 L of fluid removed) and was transferred to the ICU for hypercarbic hypoxic respiratory failure. On Day 9, (b) (6) developed severe anuric renal failure. Chest x-ray revealed worsening pulmonary edema. Also on Day 9, terlipressin was permanently discontinued due to (b) (6) SCr level of 4.8 mg/dL (baseline SCr 2.3 mg/dL). The subject was further diagnosed with multiple system organ failure due to end stage cirrhosis. RRT was not offered as the subject was not amenable to liver transplantation. On Day 9, the subject was transitioned to comfort care. On Day 12, the subject died with the reasons reported as respiratory failure, renal failure and worsened liver failure. An autopsy was not performed.

Subject 26

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 12 and MELD score of 34 at baseline and was admitted to the hospital for acute kidney injury. The subject had a medical history of stage 4 chronic kidney disease. Per protocol, the subject's terlipressin dose was increased to 2 mg every 6 hours on Day 4. On the same day, the subject had a chest x-ray which revealed moderate pneumonia versus pulmonary edema. Treatment with daily albumin stopped on Day 4; (b) (6) was previously receiving 25-100 gm/day. On Day 6, (b) (6) was found to have severe pulmonary edema, which was treated with furosemide and salbutamol. On Day 7, (b) (6) developed respiratory distress, was transferred to the ICU and intubated with high oxygen requirements. The subject was thought to most likely have aspiration pneumonitis and associated acute respiratory distress syndrome. Also on Day 7, the subject's terlipressin was discontinued due to verified HRS reversal (2 SCr 1.4 mg/dL). Later on Day 7, the subject was diagnosed with severe sepsis and

subsequently transitioned to comfort care per the family's wishes. On Day 10, the subject died with the reason reported as acute respiratory failure/distress syndrome.

Subject 27

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 7 and MELD score of 22 at baseline and was admitted to the hospital due to acute kidney injury. A chest x-ray performed 2 days before the initiation of terlipressin (Day -2) revealed very low lung volumes with possible atelectasis and dyspnea secondary to ascites. Prior to the first dose of terlipressin on Day 1, the subject experienced an episode of shortness of breath. Approximately 1 hour after the second dose of terlipressin (Day 1), the subject was found to have severe pulseless electrical activity and severe acute respiratory failure requiring intubation. On the same day, after three rounds of cardiopulmonary resuscitation, the event of pulseless electrical activity was considered resolved. On Day 4, the subject's magnetic resonance imaging revealed diffuse hypoxic brain injury. On Day 5, the subject's family requested that (b) (6) be transitioned to comfort care and (b) (6) died later that day with the reason reported as anoxic brain injury and cardiac arrest.

Subject 28

This (b) (6)-year-old (b) (6) had a Child Pugh Score of 12 and MELD score of 37 at baseline and was admitted to the hospital with abdominal distension and pain. The subject developed severe hepatic encephalopathy, severe respiratory failure requiring intubation and nonserious event of leukocytosis after 7 days of treatment with terlipressin (Day 7). The subsequent chest x-ray showed worsening of a retrocardiac opacity with left pleural effusion, raising concern for atelectasis versus consolidation. On Day 10, the subject initiated continuous veno-venous hemodialysis for fluid overload. Per protocol, terlipressin was discontinued on Day 11 due to the initiation of RRT. On Day 16, the subject died, with the reason reported as multi-organ failure.

18. Mechanism of Action/Drug Resistance Additional Information and Assessment

N/A

19. Other Drug Development Considerations Additional Information

19.1. Retrospective Application of Applicant's Proposed Risk-Mitigation Strategy

We conducted a hypothesis generating analysis on the potential effects of retrospective application of the objective mitigation criteria proposed by the Applicant (i.e., excluding subjects with serum creatinine (SCr) ≥5 mg/dL and acute-on-chronic liver failure (ACLF) grades 3) to the efficacy and safety of terlipressin as compared to placebo. There were 58 patients (29%) on terlipressin and 25 patients (25%) on placebo who did not meet the objective mitigation criteria (safety population) and were therefore, excluded from the analysis. The potential key benefits and risks based on those analyses are in the table below. Excluding this subset of patients with advanced disease and renal failure could have some impact on both safety and efficacy of terlipressin; however, we find the interpretation of this benefit-risk analysis challenging, mainly due to the untested and retrospective nature of the mitigation criteria.

Table 56. Potential Key Benefits and Risks for the Subpopulation of Subjects Who Met Objective Mitigation Criteria, CONFIRM

Application of Partial Mitigation Criteria[1]			
Benefits		**Risks**	
Benefits	**Treatment Effect (%) Terlipressin vs. Placebo (95% CI)**	**Risks (Through 30 Days After Last Dose)**	**Risk Difference (%) Terlipressin vs. Placebo (95% CI)**
Verified HRS reversal (putative surrogate endpoint)	18 (5, 30)	Any SAEs of interest	14 (5, 24)
Clinical outcomes possibly predicted by surrogate (Day 90)		Respiratory failure SAEs	4 (-4, 12)
Alive	1 (-13, 5)	Sepsis/septic shock SAEs	7 (3, 11)
No RRT	5 (-8, 18)	Abdominal pain/vomiting SAEs	4 (0, 9)
Alive post-liver transplant	5 (-2, 12)	Edema/fluid overload SAEs	2 (-3, 7)
No RRT post-liver transplant	15 (-12, 42)	Ischemia-related SAEs	1 (-1, 2)
Liver transplant (among patients listed at any point (Day 90)	-11 (-33, 10)		

Source: Reviewer analysis
[1]Analysis included subjects with ACLF Grade 0-2 and serum creatinine <5 (141 patients on terlipressin and 75 patients on control)
Abbreviations: ACLF, acute on chronic liver failure; RRT, renal replacement therapy; SAE, serious adverse event; HRS hepatorenal syndrome; CI, confidence interval

20. Data Integrity–Related Consults (OSI, Other Inspections)

20.1. Independent Data Safety Monitoring Board Meeting Discussions

A summary of the key DSMB meeting discussions is found in Table 57.

Table 57. Key Data Safety Monitoring Board Meeting Discussions

Date	No. of Subjects Enrolled	Issue/Discussion
6/29/2017	80	• "Given the large number of respiratory adverse events, the DSMB expressed its desire to follow closely all respiratory events, even though they were believed by investigators to be unrelated to the study intervention."
2/8/2018	140	• An imbalance in adverse events (AEs) (more in the terlipressin group) that was far more than the last meeting was noted. The DSMB questioned why all of the listed AEs were deemed unrelated to study drug. • A higher proportion of deaths were observed in the terlipressin group (5.7% vs. 0% in placebo group), which was not seen in previous studies.
3/26/2018		• "What has become clear is that respiratory failure is associated with a preponderance of these early deaths." • "In looking at the individual cases, the DSMB found it difficult to definitively attribute the deaths to the administration of drug because of very short duration of therapy in a vast majority of these patients." • The DSMB requested an interim report focusing on deaths and respiratory events when the next 25 subjects were enrolled and monitored for 30 days.
8/29/2018	218	• After review of data to date, the DSMB concluded that the "benefit-risk ratio remains beneficial in the Terlipressin group."
1/31/2019	267	• After the Applicant's safety update, the DSMB found the discrepancy in proportion of deaths between treatment arms (51% terlipressin vs. 40% placebo at Day 90) less worrisome compared to February 2018. • "It looks like there is a shift from hepatic-related deaths in the enrolled subjects' original disease states to cardiopulmonary-related deaths, possibly caused by vasoconstriction caused by [t]erlipressin."
5/20/2019	300	• 284 subjects' safety data were available at the time of the meeting. • "After review of the overall data up to this meeting, the concerns that DSMB had last year are no longer an issue" (i.e., higher number of deaths and respiratory events in the terlipressin arm).

Date	No. of Subjects Enrolled	Issue/Discussion
10/28/2019	300	• Study unblinded since August 2019. • "The DSMB noted that they realize the primary endpoints for this study were met, and the [*sic*] they are aware of the safety concerns. Although no significant difference was observed in rate of survival between the terlipressin and placebo groups, demonstration of the reduction in resources needed to care for the terlipressin group (ICU time, renal replacement therapy, and liver transplantation), is compelling. The DSMB believes there is a value to this intervention, which reduces hepatorenal syndrome, reduces other high costs, and reduces high-intensity medical interventions. Some adverse events occurred, but the risk benefit ratio seemed to be in the acceptable range."

Abbreviation: DSMB, Data Safety Monitoring Board; ICU, intensive care unit

21. Labeling Summary of Considerations and Key Additional Information

Deficiencies preclude discussions of labeling at this time.

22. Postmarketing Requirements and Commitments

Not applicable.

23. Financial Disclosure

Table 58. Covered Clinical Studies: MNK19013058 (CONFIRM)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 80 Principal Investigators, 390 Sub-Investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The CONFIRM trial is a randomized, double-blind, placebo-controlled, multicenter trial with an objective endpoint. Each individual site contributed a relatively small proportion of subjects to the overall trial population. The applicant was unable to obtain financial disclosure information for 5 sub-investigators involved in study conduct. The total number of subjects enrolled at sites where one or more individuals did not complete disclosure forms was 18 (6% of randomized subjects), with a majority of these subjects enrolled at sites 002 (9 subjects (3%)) and 089 (8 subjects (2.7%)). The risk to data integrity from those sites is thought to be low. The submission contains a description of the process used to collect financial disclosure information, and, based on this description, the applicant appears to have acted with due diligence to obtain the required information.

24. References

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Utako, P, T Emyoo, T Anothaisintawee, N Yamashiki, A Thakkinstian, and A Sobhonslidsuk, 2018, Clinical Outcomes after Liver Transplantation for Hepatorenal Syndrome: A Systematic Review and Meta-Analysis, BioMed Research International, 2018:5362810.

25. Review Team Acknowledgments

Table 59. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Anna Park, MS, RPh, RAC
Office of Clinical Pharmacology Reviewer(s)	Snehal Samant, PhD
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan, PhD
Clinical Reviewers	Rekha Kambhampati, MD, MHS; Tzu-Yun McDowell, PhD
Statistical Reviewer	John Lawrence, PhD
Statistical Team Leader	Jialu Zhang, PhD
Deputy Director for Safety (DCN)	Mary Ross Southworth, PharmD
Cross-Disciplinary Team Leader and Deputy Director (DCN)	Aliza Thompson, MD, MS
Division Director (OCP)	Shirley Seo, PhD
Division Director (OB)	Mark Rothmann, PhD
Office Director (or designated signatory authority)	Ellis Unger, MD

Abbreviations: DHOT, Division of Hematology Oncology Toxicology; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; DCN, Division of Cardiology and Nephrology

Table 60. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Mohan Sapru, PhD
Microbiology	Eric Adeeku, PhD
OSP/OPSA/DSAT	Leila Lackey, MHS, DEnv
OPDP	Puja Shah, PharmD
OSI	N/A
OSE/DEPI	Margie Goulding, PhD; Efe Eworuke, PhD
OSE/DMEPA	Maximilian Straka, PharmD, FISMP; Alice Tu, PharmD
OSE/DRISK	Mona Patel, PharmD; Laura Zendel, PharmD, BCPS
Clinical Team Leader	Kimberly Smith, MD, MS
Division Director (DCN)	Norman Stockbridge, MD, PhD

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DCN, Division of Cardiology and Nephrology; OSP, Office of Strategic Programs; OPSA, Office of Program and Strategic Analysis; DSAT, Decision Support and Analysis Team

Table 61. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Rekha Kambhampati	OND/DCN	IA; Appendix 12, 15, 16, 19, 20, 23 ☒ Authored ☐ Approved
Reviewer	**Signature:** Rekha Kambhampati -S Digitally signed by Rekha Kambhampati -S DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0.9 2342 19200300 100 1 1=0011837744, cn=Rekha Kambhampati -S Date: 2020 09 11 15:36:35 04'00'		
Clinical	Tzu-Yun McDowell	OND/DCN	IA; Appendix 17, 19 ☒ Authored ☐ Approved
Reviewer	**Signature:** Tzu-yun C. Mcdowell -S Digitally signed by Tzu-yun C. Mcdowell -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000563868, cn=Tzu-yun C. Mcdowell -S Date: 2020.09.11 16:08:04 -04'00'		
Clinical Pharmacology	Snehal Samant	OTS/OCP/DCEP	IA; 5, 6.1, 8.1, 8.2 ☒ Authored ☐ Approved
Reviewer	**Signature:** Snehal Samant -S Digitally signed by Snehal Samant -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Snehal Samant -S, 0.9.2342.19200300.100.1.1=2001774859 Date: 2020.09.11 15:58 33 -04'00'		
Clinical Pharmacology	Sudharshan Hariharan	OTS/OCP/DCEP	IA; 5, 6.1, 8.1, 8.2 ☒ Authored ☐ Approved
Team Leader	**Signature:** Sudharshan Hariharan -S Digitally signed by Sudharshan Hariharan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=2000394743, cn=Sudharshan Hariharan -S Date: 2020.09.11 16:02 55 -04'00'		
Biometrics	John Lawrence	OB/DB1	IA; 6.2, 6.3 and 6.4 ☒ Authored ☐ Approved
Reviewer	**Signature:** John P. Lawrence -S Digitally signed by John P. Lawrence -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144280, cn=John P. Lawrence -S Date: 2020.09.11 15:53:22 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Jialu Zhang	OB/DB2	IA; 6.2, 6.3 and 6.4 ☒ Authored ☐ Approved
Choose title/role	**Signature:** Jialu Zhang -S Digitally signed by Jialu Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jialu Zhang -S, 0.9.2342.19200300.100.1.1=1300369843 Date: 2020.09.11 16:30:50 -04'00'		
Biometrics	Mark Rothmann	OB/DB2	IA; 6.2, 6.3 and 6.4 ☐ Authored ☒ Approved
Division Director	**Signature:** Mark D. Rothmann -S Digitally signed by Mark D. Rothmann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144907, cn=Mark D. Rothmann -S Date: 2020.09.11 16:48:24 -04'00'		
Clinical	Mary Ross Southworth	OND/DCN	IA ☐ Authored ☒ Approved
Team Leader	**Signature:** Mary R. Southworth -S Digitally signed by Mary R. Southworth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300234574, cn=Mary R. Southworth -S Date: 2020.09.11 16:14:34 -04'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary; OND, Office of New Drugs; DCN, Division of Cardiology and Nephrology; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; OTS, Office of Translational Sciences; DB1, Division of Biometrics 1; Division of Biometrics 2; DCEP, Division of Cardiometabolic and Endocrine Pharmacology

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANNA J PARK
09/11/2020 04:55:11 PM

ALIZA M THOMPSON
09/11/2020 05:00:02 PM

ELLIS F UNGER
09/11/2020 05:06:15 PM

Office Director Decisional Memo

Date	4 November 2009
From	Ellis F. Unger, M.D., Deputy Director, ODE-1
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	22-231 0000
Applicant Name	Orphan Therapeutics, LLC
Date of Submission	5/4/09
PDUFA Goal Date	11/4/09
Proprietary Name / **Established (USAN) Name**	Lucassin Terlipressin
Dosage Forms / Strength	Preservative-free lyophilized powder for injection; 0.85 mg per glass vial
Proposed Indication(s)	Hepatorenal Syndrome (HRS) Type I
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Shari Targum
Medical Officer/Statistical Review	Nancy Xu/John Lawrence
Pharmacology Toxicology Review	Gowra Jagadeesh, Charles Resnick
CMC Review	Shastri Bhamidipati, Ramesh Sood
Biopharmaceutics Review	Gowra Jagadeesh
Clinical Pharmacology Review	Divja Menon-Anderson, Pravin Jadhav, Rajanikanth Madabushi
Microbiology	Vinayak Pawar, StephenLangille
DSI	Sharon Gershon
OSE/DMEPA	Anne Crandal
QT Interdiciplinary Team	Suchitra Balakrishnan
Immunogenicity, Division of Therapeutic Proteins	Melinda Bauerlien, Michael Phelan, Daniela Verthelyi

ODE-1= Office of Drug Evaluation I
OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
CMC=Chemistry manufacturing Controls
DSI=Division of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Concurrence
I concur with the recommendation of Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products, on a Complete Response action for terlipressin, NDA 22-231. The review team is aware of the planned action, and is aligned on this decision.

Background
Terlipressin is a new molecule entity (NME), a 12-residue synthetic peptide with a single disulfide bond. It is a vasopressin analogue with agonism for the V_1 receptor. The proposed indication is "treatment of patients with hepatorenal syndrome (HRS) type 1."

Hepatorenal syndrome (HRS) is a condition of significant renal impairment that occurs in patients with advanced cirrhosis. It is thought to result from reduced effective plasma volume, due in part to splanchnic arterial vasodilation and renal arterial vasoconstriction. Reduced cardiac output and endothelial dysfunction may also be involved in the pathophysiology. Often fatal, the only definitive treatment of HRS is liver or liver-kidney transplantation; the primary goal of management is to provide a bridge to liver transplantation. There are no approved treatments for HRS in the U.S. Colloidal volume expanders (albumin) and various vasoconstrictors (midodrine and octreotide, alone and in combination) are typically used, but results have been inconsistent. Terlipressin is approved in some countries for HRS (Ireland, South Korea, and France), and in a broader range of countries for the treatment of acute esophageal variceal hemorrhage.

Chemistry
Although the concerns do not appear inherently serious, there are, nonetheless, a number of CMC issues in need of resolution. The requests to be communicated to the applicant are: (b) (4)

(b) (4)

Pharmacology/Toxicology
All adverse effects appeared to be related to exaggerated pharmacodynamic activity, i.e., V_1 receptor-mediated vasoconstriction.

Clinical Pharmacology
Terlipressin's pharmacokinetics have been studied in normal volunteers and through sparse PK sampling in HRS patients. The half-life is about an hour in both patients and normal volunteers. Terlipressin is degraded by tissue peptidases; essentially none is excreted. Terlipressin has no effect on CYPs, *in vitro*.

Per agreement with the Division, the applicant did not perform a thorough QT study, but collected ECGs in the principal efficacy study, OT-0401. ECGs were to be obtained at baseline, at Days 3 and 7, and Day 14 or end-of-treatment. Two ECGs were to be recorded, 30 minutes apart. The QT Interdisciplinary Review Team (QT-IRT) could not come to any conclusions regarding the ECG data or cardiovascular adverse events from Study OT-0401, due to design issues, confounding conditions, and analytic problems. Because patients with HRS are critically ill and intensively monitored, however, the QT-IRT thought the evaluation

was probably adequate. The IRT suggested that the label should convey caution in patients with hypokalemia, hypomagnesemia, and with concomitant use of medications that prolong QT. They noted that telemetric ECG monitoring could be recommended.

Immunogenicity
The applicant concluded that no significant anti-terlipressin antibodies had been detected in samples of subjects in the phase 3 program; however, the Division of Therapeutic Proteins deemed the applicant's assay to be unacceptable, rendering the data largely uninterpretable. The Division of Therapeutic Proteins has transmitted advice to the applicant to help them improve the assay. Reassuring points include: 1) peptides of small size are not generally immunogenic; 2) the intravenous route of administration tends to be less immunogenic than others; and 3) the potential for re-administration of the product (beyond 2 weeks) seems remote. Had the application been otherwise approvable, and particularly if the drug had shown a clinically important benefit, the lack of an adequate assessment of immunogenicity might have been deferred.

Evidence of Effectiveness
The evidence of effectiveness has been addressed by Drs. Xu, Lawrence, Targum, and Stockbridge. The applicant submitted two clinical trials, OT-0401 and TAHRS.

OT-0401
OT-0401 was a randomized, placebo-controlled, double-blind study of 112 subjects with HRS-Type I. The vast majority of the 35 sites were domestic. The original per-protocol 1° endpoint was "treatment success" at Day 14, defined as percentage of subjects alive with serum creatinine $\leq$ 1.5 mg/dL with $\geq$ 2 measurements 48±2 hours apart. The 1° analysis was to be conducted on a modified intent-to-treat (mITT) population, defined as subjects who did not receive a liver transplant prior to reaching the endpoint.

The original protocol included an interim analysis for which some alpha was allocated, but the interim analysis was removed by protocol amendment #2, 9/15/05. Protocol amendment #3 (2/24/06) changed the verification requirement for serum creatinine from 48±2 hours to 48±8 hours.

Results: For the prospectively planned mITT analysis, rates of "treatment success" were 14/48 (29%) on terlipressin and 7/44 (16%) on placebo, p=0.13. The applicant conducted a post hoc analysis that counted, as a "treatment success," subjects who had not received a transplant or dialysis and who had achieved even a single creatinine value $\leq$ 1.5 before the last non-missing dose of study medicine. Using this definition, the applicant was able to reclassify 5 additional subjects in the terlipressin group as a "treatment success," which lowered the p-value to 0.008. Even if the post hoc change in the definition of "treatment success" had been acceptable, the review team disagreed with the applicant's reclassification and removed 2 re-defined "treatment successes" from the terlipressin group (subjects who died or had HRS recurrence), and added 1 "treatment success" to the control group (a subject who had undergone a transplant, but achieved a creatinine $\leq$1.5 mg/dL prior to transplant). With these changes, the p-value was 0.068. Ultimately, the applicant performed additional post hoc analyses, seeking out additional creatinine values in subjects who were close to reaching a creatinine of 1.5 mg/dL, in an attempt to show a more robust finding. (These data had not been recorded in the case report forms.) Due to the exploratory nature of the post hoc analyses, no one on the review team found the efficacy results convincing.

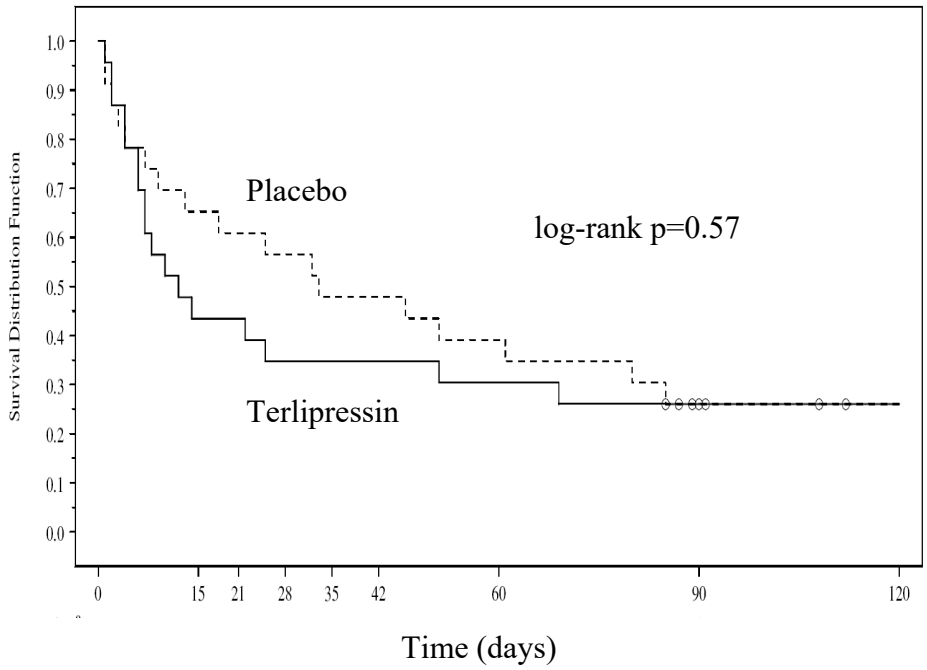
Moreover, despite the relative simplicity of the protocol and what should have been a straightforward 1° endpoint based on a laboratory measure, the review team identified a number of important shortcomings:

- Poor documentation of inclusion criterion to establish diagnosis of HRS Type I
- Post-treatment serum creatinine values used as “baseline” values in some subjects
- Erroneous (overly stringent) definition of proteinuria due to an error in the original protocol; This may have permitted enrollment of subjects with intrinsic renal disease who would not have met diagnostic criteria for HRS.
- Potential exclusion of creatine values: many values were obtained that were not reported in the case report forms. The extent to which the applicant may have selected and/or excluded values for analysis is uncertain.
- Inability to distinguish subjects with HRS Types I and II, due to lack of creatinine assessments within 2 weeks prior to HRS diagnosis

TAHRS

TAHRS was planned as a phase 4 study for the European Union, and presumably a confirmatory study for U.S. registration. This was an open-label study of 46 subjects (out of a planned N of 100) with HRS Types I and II, conducted in Spain. The prospectively planned 1° endpoint was survival at 90 days. The results were confounded by substantial crossover of control subjects (11 of 23, 48%) to terlipressin. The study was stopped early, presumably for futility and/or a negative trend on mortality. Survival at 90 days was 26% in both groups; however, earlier in the study, more proximal to the time of terlipressin administration (mean exposure was about a week), the mortality results trended negatively for terlipressin (Figure 1).

Figure 1: TAHRS – Sponsor’s Kaplan Meier Plot of Overall Survival (ITT Population)



Efficacy Summary

Study OT-0401 has a number of shortcomings and failed on its prespecified 1° endpoint. The applicant's post hoc analyses are not compelling. Nevertheless, the study does appear to show some evidence of terlipressin's biologic activity in HRS, based on changes in creatinine. The Division is willing to consider OT-0401 as a *supportive* study, i.e., one of two studies needed for approval. The applicant will need to show evidence of efficacy in a second study that provides a clear "win" on a prespecified 1° endpoint with a solid, prospectively planned, analytic plan.

Clinical Safety

As pointed out by Dr. Stockbridge, the small size of the development program provides little reassurance regarding safety. In fact, there were only 11 subjects in OT-0401 and 9 subjects in TAHRS (total n = 20) who received a full 14-day course of terlipressin, yet the proposed labeling recommends treatment for up to 14 days. Even recognizing that this is an orphan disease, the size of the safety database seems insufficient.

Dr. Stockbridge notes that there are no obvious safety issues in the development program. That is probably true, in that it would be difficult for *anything* to be obvious in this patient population, particularly given the size and depth of the safety experience. Nevertheless, I think there are some safety issues that merit concern.

Terlipressin's mechanism of action is to cause vasoconstriction through V_1 receptor agonism. As such, it is expected to redistribute perfusion, and has the potential to cause tissue ischemia and/or necrosis. The review team was unable to characterize adequately the hemodynamic effects of the drug. Possibly this was because the OT-0401 protocol directed that vital signs would be collected at baseline and then only 2 hours after each dose. (In the TAHRS study, vitals were obtained once each day, and the time of collection relative to administration of study drug was not recorded.) Unfortunately, therefore, the studies made no real attempt to assess blood pressure effects when serum concentrations were at their peak (C_{max}). In a recently published study evaluating subjects with cirrhosis (Narahara Y, et al., J Gastroenterol Hepatol. 2009 Aug 3. [Epub ahead of print]), terlipressin (n=19) increased mean arterial pressure from 88±11 to 103±12 and decreased cardiac output from 5.7±1.4 to 5.0±1.2. This represents an increase in systemic vascular resistance of approximately 35%. (There were no hemodynamic effects in a placebo group.) It would seem worthwhile to better characterize the hemodynamic effects of terlipressin in HRS patients in an additional study, specifically to monitor blood pressure effects at C_{max}. (Note, because of the above concerns, the pharmacodynamics section of labeling, Section 12.2, should probably be revised with new data. Also, the need for better data will be included in the CR letter.)

According to primary clinical/statistical review (page 34), there were 2 subjects in OT-0401 who experienced "cardiac arrest," and one myocardial infarction (MI). All 3 were in the terlipressin group. Subject (b) (6) experienced cardiac arrest "…due to hepatic insufficiency" and died less than 2 hours after receiving 2-mg terlipressin. A second subject (b) (6) also sustained a cardiac arrest and died 3 hours after receiving the second dose of terlipressin. The subject with an MI had a complicated course that is difficult to interpret. There was also a subject in the terlipressin group who experienced intestinal ischemia versus none in control. The trend showing increased all-cause mortality in TAHRS is also concerning. In both

studies, the numbers of adverse events are small - - not unexpected given the small sample sizes. The problem, however, is that there is mechanistic plausibility here: terlipressin would be expected to decrease perfusion in some vascular territories, which could lead to regional or local ischemia with adverse consequences.

Dr. Targum noted that there were 6 subjects in the terlipressin group of study OT-0401 with bronchospasm or wheezing, versus none in the control group. Although they raise concern about possible allergic reactions, all 6 were classified as non-serious adverse events, and there were no other adverse events in the dataset that suggested allergic reaction, although such symptoms should be carefully sought if there is an additional clinical trial.

Finally, it is noteworthy that the OT-0401 protocol did not include collection of complete blood counts (CBCs) in the monitoring scheme; TAHRS required a CBC at baseline, Day 7 and Day 15. For completeness, it would be prudent to obtain such data if the applicant decides to undertake an additional registrational trial, and this will be included in the CR letter.

Summary and Conclusions

For all of the reasons above, I agree with the recommendation of Dr. Norman Stockbridge and the review team, to take a CR action on this NDA. These conclusions and concerns will be transmitted to the applicant in a Complete Response Letter.

Applicant's Path Forward

The applicant will need to conduct another efficacy study. The 1° endpoint and analytic plan should be discussed with and agreed upon by the Division prior to initiation.

The review team has pointed out that the clinical significance of a mere change in creatinine, even if durable, is somewhat dubious in this setting, especially if it must be balanced against even a few excess ischemic events.

Ideally, one would want the applicant to show improvement in an outcome, which could be resolution of HRS or successful bridging to transplant. The problem with the former is that the primary derangement in HRS is hepatic, and terlipressin is not expected to improve that. The problem with the latter lies in the operational definition of "candidacy." Presumably, one would try to enroll subjects who are <u>not</u> candidates for transplant, and aim to improve their status so that they <u>become</u> candidates. Given the complex decision-making involved here, however, use of transplant candidacy as a 1° study endpoint seems challenging.

It would not be difficult to design a study to show an unequivocal and durable effect on serum creatinine, and this is probably the best path forward for establishing efficacy. An endpoint of creatinine $\leq$1.5 mg/dL (or some other marker; some other value), that was present at Day 15 and confirmed subsequently (ideally off-drug, to rule out acute drug-related effects), would be feasible. Subjects who require dialysis or die with creatinine >1.5 mg/dL would be counted in the denominator, but would not be counted as successes. Subjects who undergo hepatic transplant would be worth some additional thought. (Perhaps the applicant got it right - - these patients should be removed from the denominator.) As Dr. Stockbridge points out, all of these issues should be discussed before the protocol is written, perhaps at an advisory committee meeting.

Finally, in my view, the safety database for this application would have been insufficient even if OT-0401 had shown a statistically persuasive and durable effect on serum creatinine. Given the adverse signals detected at this juncture, the overall size of the safety database should be an important topic of discussion with the sponsor prior to initiating another study.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
11/04/2009

COMBINED CLINICAL AND STATISTICAL REVIEW

Application Type	NDA
Submission Number	22,231
Submission Code	000, 033, 034, 036, 037
Letter Date	May 27, 2008
Stamp Date	May 27, 2008
PDUFA Goal Date	November 4, 2009
Clinical Reviewer Name	Nancy Xu
Statistical Reviewer Name	John Lawrence
Review Completion Date	11-4-09
Established Name	Terlipressin
(Proposed) Trade Name	Lucassin
Therapeutic Class	Vasopressin Analogue
Applicant	Orphan Therapeutics
Priority Designation	Rolling Submission
Formulation	IV
Dosing Regimen	Every (b) (4) 6 hours for up to 14 (b) (4) days
Indication	Hepatorenal Syndrome (HRS) Type I
Intended Population	Patients with HRS Type I

THIS REVIEW VERSION REPLACES THE PREVIOUS TWO VERSIONS DATED FEBRUARY 5, 2009 AND OCTOBER 20, 2009, RESPECTIVELY.

TABLE OF CONTENTS

1 Recommendations/Risk Benefit Assessment

From the clinical and statistical perspectives, we recommend that terlipressin should not be approved for hepatorenal syndrome (HRS) type I. Based on the data submitted for this application, at least one additional adequate and well-controlled study is necessary to demonstrate the efficacy and safety of intravenous administration of terlipressin for the treatment of type I HRS.

We are recommending non-approval of this application for a number of reasons. To support the claim, the sponsor submitted two studies, OT-0401 (double-blind, placebo-controlled study in HRS type I patients) and TAHRS (a small open-label, cross-over study in HRS I and II patients). Neither study met its pre-specified primary endpoint. In OT-0401, the single pivotal trial, terlipressin as compared to placebo had a modest and transient reduction in serum creatinine (SCr), but failed to achieve a sustained effect on SCr beyond 40 hours. Moreover, terlipressin treatment failed to reduce the incidence of dialysis or death. Similar to OT-0401, trial TAHRS did not demonstrate a sustained effect on SCr. Furthermore, the sponsor did not submit data on the endpoint that they had pre-specified (i.e. survival at 90 days). Therefore, no convincing clinical benefit has been demonstrated.

With regard to risks associated with terlipressin treatment, in both studies, the terlipressin treatment arm had more treatment-emergent adverse events (TEAE) compared to placebo. Hypothetically, some of the TEAEs with terlipressin (i.e. myocardial infarction) can conceivably prevent or delay one's chance for the definitive therapy, liver transplant. This hypothesis is supported by the observation that the chance of receiving a liver transplant appears no different with terlipressin as compared to placebo, despite a transient reduction in SCr. In summary, in the reviewers' opinion, a net favorable benefit to risk balance has not been convincingly demonstrated.

Lastly, the following key deficiencies in the conduct of OT-0401 limit the utility of the data for assessing the nominal effect of the terlipressin on SCr in the intended population.

- There was a lack of a uniform process for establishing "baseline" SCr. Baseline SCr were obtained before or after a patient qualified as having HRS type I, or even after the first dose of study medication. This affects the validity of results of the change from baseline in SCr analyses.
- Incomplete and inaccurate documentation of the screening assessment (i.e. proteinuria) makes it unclear if the study population met the intended eligibility criteria. Because HRS is a diagnosis of exclusion, poor adherence to eligibility criteria may allow for inclusion of subjects with other disease processes (i.e. reversible pre-renal state or acute tubular necrosis). In a small study, this can affect the validity of the study outcome.
- For patients who stopped treatment within the 14-day study period because of treatment response, treatment failure, adverse event, or investigator decision, SCr values were at times no longer collected. The large amount of missing SCr values within the pre-specified 14-day treatment period poses difficulties with regard to the interpretation of the SCr analyses.

2 Introduction and Regulatory Background

2.1 Product Information

Terlipressin, a vasopressin analogue, is a selective vasopressin-1 agonist.
Terlipressin is the established name and the proposed trade name is (b) (4)

Chemical class: Triglycyl Lysine Vasopressin; amino acid synthetic analogue of lysine-vasopressin. Terlipressin itself is inactive, but is transformed into its biologically active form by endo- and exopeptidases to vasopressin.

Pharmacologic class: A systemic vasoconstrictor that acts through the vasopressin V_1 receptors.

The sponsor's proposed indication is for treatment of type I hepatorenal syndrome (HRS). The proposed administration is intravenous injection.

The sponsor's proposed dosing regimen is as follows:

- 1 mg (as a IV bolus over 2 minutes) every 6 hrs for up to 14 days,
- If after 3 days SCr is not reduced by ≥30% then increase to (b) (4) mg every 6 hrs
- Discontinue 2 days after SCr ≤1.5mg/dL or after 14 days of therapy.

(b) (4)

Proposed age groups for treatment: patients (b) (4) 18 years of old.

2.2 Tables of Currently Available Treatments for Proposed Indications

HRS describes a condition that typically occurs in end-stage liver disease where the renal impairment seems to be driven by the circulatory changes of the underlying liver failure. In HRS, kidney tubular function is intact and renal impairment is reversed by liver transplantation. There is currently no specific diagnostic test to verify HRS. As renal impairment in HRS is thought as the sole consequence of the circulatory changes in end stage liver disease, it remains a diagnosis of exclusion.

Diagnostic criteria for HRS were proposed by International Ascites Club (IAC) consensus conference and used in clinical trials. According to the International Ascites Club, HRS is defined by the presence of five criteria: (1) severe cirrhosis; (2) glomerular hypofiltration; (3) no other functional or organic causes; (4) failure of plasma volume expansion; (5) no proteinuria. HRS is further sub-categorized into types I and II based on the rate and severity of renal function deterioration. Type I HRS is defined by a significant decline in renal glomerular filtration within two weeks and characterized by a high mortality rate, with median survival time of less than two weeks. Type 2 HRS, typically occurring in patients with relatively preserved liver function, has

a more protracted course with less severe renal impairment, appears to be more responsive to interventions in circulatory parameters and has a longer survival.

Currently, the only treatment with survival benefit for HRS is liver transplantation. There is no FDA-approved pharmacologic treatment for HRS, and no therapy has been shown to produce clinically meaningful improvements in renal function or survival. Medical therapies target the postulated circulatory changes in HRS. According to current theories, cirrhosis leads to splanchnic artery vasodilation which ultimately results in renal artery vasoconstriction and development of renal impairment. Systemic vasoconstrictor drugs have been used in HRS to oppose the extreme dilatation of splanchnic arterial bed. The interventions for HRS are shown in Table 1 below.

Table 1. Interventions for Hepatorenal Syndrome.

Plasma Expander- to maintain central and renal hemodynamic variables Albumin
Systemic Vasoconstrictor Midodrine Octreotide Norepinephrine Terlipressin Ornipressin
Renal Vasodilators Have fallen out of favor due to lack of effect
Non-Medical Intervention Peritoneovenous shunts Extracorporeal liver support therapy Dialysis, mainly used as a bridge to liver transplantation

2.3 Availability of Proposed Active Ingredient in the United States

Terlipressin is not currently available in the U.S., although it is available in a number of other countries (see Section 2.6).

2.4 Important Safety Issues with Consideration to Related Drugs

Systemic administration of an earlier vasopressin analogue, ornipressin, for HRS has been largely abandoned due to the high incidence of severe ischemic complications. Ornipressin is not available in the US. In other countries, systemic administration of ornipressin is available to treat esophageal variceal bleeding and local administration to induce ischemia and hemostasis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 A Chronological Outline of Major Presubmission Regulatory Activities:

Date	**Key milestones**	**Main discussion points**
1/22/04	Pre-IND meeting	▪ The sponsor should verify that the HRS type I definition is identical to the historical definition when using historical data to support approval. ▪ The sponsor was encouraged to look at sample size, include an interim analysis, and make adjustments accordingly. ▪ Other recommendations: Six-month mortality data, assessment of MELD score and encephalopathy, studying more than one dose, analyzing the primary endpoint using MITT and ITT populations.
	Pre-IND teleconference	▪ FDA expressed concern about mandating background albumin therapy as albumin is not approved in this indication. ▪ FDA expressed concern about alpha = 0.05 was too high given the need for this single trial to be highly convincing. If the literature describes a different population and/or were difficult to interpret, then Agency suggested an alpha < 0.01.
10/29/04	Orphan drug designation granted.	
4/5/05	Fast-track status granted.	
11/22/06	Pre-NDA meeting	▪ FDA stated that OT-0401 findings are not compelling; the primary endpoint failed to show statistical significance at $p < 0.05$. ▪ Should the sponsor plan on a confirmatory study, Agency recommended that they conduct a double-blind study. ▪ FDA agreed that "HRS reversal was a reasonable endpoint but it cannot be defined as a one-time SCr improvement that then goes away." ▪ FDA informed the sponsor that they should plan on demonstrating effectiveness on the primary endpoint, a sustained improvement in SCr, in two studies at $p<0.05$. ▪ The sponsor planned to obtain data to an already conducted TAHRS's trial with terlipressin to be included in their NDA submission. ▪ FDA agreed to a rolling review.

2.6 Other Relevant Background Information

Based on the sponsor's translated foreign drug labeling, terlipressin is approved for the treatment of hepatorenal syndrome in France, Ireland, and South Korea. These approvals were apparently based on published literature. Per the sponsor's translated material, common side effects include ischemic and respiratory complications. Cases of pancreatitis were also reported.

Terlipressin is approved in a number of countries outside the U.S., for the treatment of acute esophageal variceal hemorrhage.

Based on an internet search (10/1/2008), terlipressin has not been withdrawn from the market in any country due to safety concerns.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Problems with Submission Organization and Quality:

This was a rolling submission, and therefore, the reviewers could not refuse to file the application. The original paper submission was missing the index for the key documents of the pivotal trial (e.g. protocols and statistical algorithms documents). In sections where indexing was available, the page number was sometimes missing or mismatched with the index (e.g. algorithm document). In addition, the dataset for both studies, OT-0401 and TAHRS, contain non-standard format of data entry (e.g. dates were entered in character format in the AEDOSE dataset). TAHRS's dataset was available upon request for review on 10/7/2008. Multiple subsequent queries were required for additional information and/or clarification on study reports and datasets.

Problems with Data that Limit Interpretation of the Results:

1. Insufficient Information to Determine Whether Subjects Met HRS I Diagnostic Criteria

a) Non-adherence to IAC HRS type I criterion #1, a doubling of SCr concentration >2.5 mg/dL within two weeks

Based on the original OT-0401 electronic dataset, 19 (9 in terlipressin and 10 in placebo arm) out of the 112 enrolled subjects did not have the initial and qualifying SCr measurement done within two weeks (median 23 days, interquartile range [IQR] 19 days). For these subjects, the medical reviewer can not determine if the rapidity of renal function decline was consistent with diagnostic criterion #1.

b) Missing initial SCr to verify HRS type I diagnostic criterion #1

Please see analysis section.

c) Missing documentation to ensure adherence to IAC diagnostic criterion for HRS #4, no sustained improvement in renal function after diuretic withdrawal and plasma volume expansion with 1.5 liter isotonic saline

A failure of plasma volume expansion is a HRS diagnostic criterion intended to rule out pre-renal etiologies as an alternative and a more reversible cause of renal

impairment. For all study subjects, the sponsor "does not have specific information on file regarding the exact quantity and timing of IV fluid administration" during the screening period to verify the fulfillment of HRS criterion #4.

d) Non-adherence to proteinuria <500mg/d, IAC diagnostic criterion for HRS

On the original inclusion criteria form, a lack of significant proteinuria was erroneously defined as having less than 500 mg/*dL* instead of less than 500 mg/*day*. As a result, subjects with significant proteinuria and intrinsic renal disease could have been enrolled. Although this typographic error was corrected in the protocol amendment on 9/12/2005, the medical reviewer found the erroneous proteinuria criterion often remained on the case report forms (CRFs) for subjects enrolled after that date (e.g. 182-04). Furthermore, without having the appropriate proteinuria tests performed and/or urine output information collected at the time of randomization, one can not extrapolate total amount of protein per day (mg/day) to verify if appropriate subjects were included.

With the above limitations, the medical reviewer frequently could not determine whether subjects met the diagnostic criteria for type I HRS, nor the distribution of subjects who actually met the diagnostic criteria between the two treatment groups.

2. Non-uniform determination of baseline SCr value

Per the OT-0401 protocol, a baseline SCr value was defined as the "latest non-missing (SCr) value" after study qualification but before starting study medication or "pre-study period" if the former is missing. However, the sponsor subsequently acknowledged that the OT-0401 trial lacked a uniform screening process and some sites "recorded a qualifying SCr before" patients met all inclusion criteria. In the study population with rapidly declining renal function, 44 (39%) enrolled subjects (terlipressin [n=20], placebo [n=24]), there were significant time intervals (up to 14 days) between qualification and the start of the study treatment. In addition, 11 subjects (terlipressin [n=5], placebo [n=6]) had baseline SCr values recorded before qualifying for the study; 3 subjects (b) (6) s pre-treatment baseline SCrs were instead post-treatment Day 1 SCrs.

This variation in identifying the baseline creatinine value with respect to that of HRS type I qualification and study medication commencement is problematic for two reasons. First, it could potentially introduce systematic bias, particularly for the two secondary endpoints that directly incorporate baseline SCr as a reference for treatment effect: the change from baseline in SCr and the incidence of treatment failure. Moreover, the study protocol does not mitigate against regression toward the mean in SCr. Both issues can undermine the study results.

3. Missing SCr values in dataset to allow independent verification of treatment effect for all efficacy endpoints based on SCr

The sponsor submitted datasets with only SCr values used in their analyses, not all SCr measurements performed on study treatment. The medical reviewer found SCr measurements

that were performed according to the OT-0401 CRFs, but not included in the datasets for analysis. Furthermore, the reason for excluding certain SCr measurements from the analyses was at times not clear to the reviewer (e.g. 131-01). This concern is not completely addressed by the sponsor subsequently submission of additional SCr values identified from a retrospective review of subjects who had serum creatinine close to 1.5 mg/dL within the pre-specified Day 14 period.

4. The SCr outcome for terminating dosing in the clinical protocol was not followed by investigators

According to the sponsor's pre-specified clinical protocol, dosing should be terminated when SCr ≥ baseline at Day 7 or later. Many patients were discontinued for "not much improvement in SCr" before Day 7 (the sponsor's appendix 8.2.13 in response to FDA question 10/12/09). Furthermore, this early termination of study treatment outside the protocol definition for "treatment failure" was found only in the placebo group (b) (6) This might undermine the validity of the nominal effect of the drug on SCr.

5. Dose is not titrated per clinical protocol

In the pivotal trial, OT-0401, there are many cases (b) (6) when doses were not up-titrated per the clinical protocol, which forms the basis for the drug label. This undermines the ability to write dosing instructions based on the trial.

6. Dose date and time discrepancy between dataset and CRF

Discrepancies between the last dose date and time in CRFs versus the DOSE dataset were noted (b) (6) Without accurate information on the timing of the dosing, it can be difficult to reliably identify treatment emergent AE or withdrew due to AE.

7. Inconsistent OT-0401 survival information might undermine the accuracy of the survival analysis

Subjects (b) (6) (placebo), (b) (6) (placebo) and (b) (6) (terlipressin) have different death dates in CRFs than the dataset used for survival analysis. Subject (b) (6) (placebo), (b) (6) (terlipressin), (b) (6) (terlipressin), and (b) (6) (terlipressin)'s listed death dates in the dataset were not documented on the CRFs.

8. Improper attribution of adverse events to placebo in subjects who later crossed-over to terlipressin treatment

During review of the available study reports for what sponsor deemed as serious AE, this medical reviewer found four subjects, (b) (6) who were originally assigned to placebo group but later received open-labeled terlipressin therapy. All above subjects had serious AEs attributed to placebo therapy even when events occurred after placebo was discontinued and during the terlipressin therapy. The sponsor did not provide the identities of all placebo subjects who had later crossed-over to open-labeled terlipressin therapy. Therefore, the medical reviewer can not determine the prevalence of the improper attribution of AE.

3.2 Compliance with Good Clinical Practices

The sponsor claims to be compliant with good clinical practices.

3.3 Financial Disclosures

The sponsor certified that he (Peter Teuber) has not entered into any financial arrangements with listed clinical investigators in OT-0401 and TAHRS. The sponsor also discloses that the clinical investigators did not have any conflict of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This is a rolling NDA submission. The first section that was submitted was the clinical portion which has been reviewed by the Division. One pharmacokinetic dataset, NM2A, was submitted in isolation and in non-standardized format (with missing description of variables, dosing information). The clinical pharmacology review is not currently available.

4.1 Clinical Pharmacology

Mechanism of Action

Terlipressin is a systemic vasoconstrictor, via vasopressin V_1 receptors.

Pharmacodynamics

Per the sponsor's proposed labeling, terlipressin increases MAP and decreases heart rate while increasing systemic vascular resistance.

Pharmacokinetics

Per the sponsor's proposed labeling, (b) (4)

(b) (4)

5 Sources of Clinical Data

The source of clinical data was the clinical trials below (see

Table 3). This submission included electronic study reports, available SAS data sets and case report forms (CRFs) for OT-0401 and TAHRS.

5.1 Tables of Clinical Studies

The Sponsor provided a single pivotal Phase 3 study and one open-label safety study (see Table 3) in support of their proposed indication.

Table 3. Summary of Clinical Studies

Study	Design	Sites	Drug (N)	Control (N)	Outcome
PIVOTAL STUDY OT-0401/	double-blind, randomized, placebo controlled	USA (30), Russia (3), Germany (2)	Terlipressin 4-8 mg/d (IV q 6h) up to 14 days +/- Albumin: 100 g on Day 1, then 25g/d up to 14 days (N=56)	Mannitol (11mg/6mL) Same dose regimen +/- Albumin: 100 g on Day 1, then 25g/d up to 14 days (N=56)	Treatment success at Day 14 Survival
SAFETY STUDY TAHRS/ (designed and conducted for publication purpose only)	Open-label, randomized, albumin-controlled placebo group was allowed to cross-over to terlipressin* HRS I and II	Spain (9)	Terlipressin: 3-12 mg/d (IV q4h) and Albumin: (20-40 g/d) up to 15 d (17 HRS I) (6 HRS II)	Albumin (20-40 g/d) up to 15 d (HRS I /HRS)	HRS Reversal Survival

Protocol amendment: see individual study review for further details

5.2 Review Strategy

The medical reviewer reviewed the Protocols, the Protocol Amendments, Administrative Letters, Clinical Study Reports, datasets, and CRFs for OT-0401 and TAHRS. This reviewer performed additional analyses as necessary using JMP.

5.3 Discussion of Individual Studies

5.3.1 Pivotal Study OT-0401:

Title: A Double-Blind, Placebo-Controlled, Randomized Phase 3 Study of Intravenous Terlipressin in Patients with Hepatorenal Syndrome Type 1

Primary Objective: To demonstrate that intravenous (IV) terlipressin is safe and effective in the treatment of patients with hepatorenal syndrome (HRS) type 1 when compared with placebo.

Table 4 . OT-0401: Timeline of Protocol, Key Amendments and Change in Endpoints

Date	Protocol, Amendment, and Change in Endpoints
3/25/04	The original protocol finalized
7/16/04	▪ Corrected typographical error in inclusion criteria: From "chronic liver disease *AND* acute liver disease" To "chronic liver disease *OR* acute liver disease"
9/12/05	▪ Deleted interim analysis that was intended to adjust sample size ▪ Changed the secondary endpoint, "The Incidence of Partial Response" to **"**The Incidence of Achieving At Least a Partial Response". ▪ Clarified that serious adverse events (SAE) reporting, with the exception of death, continued for 30 days following treatment termination. All death was recorded as SAE for 180 days post treatment termination. ▪ Corrected the proteinuria unit from <500 mg/dL per day to <500 mg per day in the inclusion criteria, to be consistent with the IAC definition of HRS. Expanded the need for dialysis data collection through the 180 day follow-up.
9/22/04	First patient enrolled.
2/24/06	▪ Changed the time span of the sustained improvement in SCr from 48 ± 2 (aka ≥ 46) to 48 ± 8 (aka ≥ 40) hours apart in the primary endpoint, Treatment Success at Day 14. ▪ To analyze the incidence of dialysis and the number of days on dialysis at the following five time points: up to 14, 30, 60, 90 and 180 days. ▪ To analyze the overall survival and transplant-free survival at the following five time points: 14, 30, 60, 90 and 180 days.
3/10/06	Last patient enrolled.
6/12/06	Database closure and unblinding per sponsor report
8/28/06	Last patient completed 180-day follow-up.
8/31/06	▪ Finalized HRS reversal, a "post hoc" primary endpoint, which was a one-time reduction in SCr. Unlike the pre-specified endpoints (e.g. treatment success, treatment failure, combined partial response), HRS reversal included subjects with HRS recurrence. ▪ Defined HRS recurrence as any SCr measurement of >2.5 mg/dL after the initial SCr ≤1.5 mg/dL.

Randomization:
Patients were randomization 1:1 to treatment groups via an interactive voice response system. Patients were stratified by alcoholic cirrhosis. Randomization codes were generated by the statistician and were not accessible to the sponsor, investigators or other site personnel until the clinical database, including the 3 month follow-up period, was closed.

Blinding:
The active and placebo vials were labeled with single panel labels comprised of the randomized identification numbers for each kit to maintain the blinding of the randomization treatments.

OT-0401 Inclusion criteria incorporating the amendments:

- Over 18 years of age
- Chronic liver disease OR Acute liver disease, defined as de novo onset within 6 weeks; e.g. viral and/or alcoholic hepatitis (AH).
- HRS type I, defined using International Ascites Club diagnostic criteria as specified below (module 5, volume 10/37, section 4.2):
    - A rapidly progressive decline in renal function: a doubling of SCr concentration >2.5 mg/dL OR a 50% reduction of the initial 24 hour creatinine clearance, OR to a level lower than 20 mL/minute within two weeks.
    - Low "GFR", as indicated by a SCr >1.5 mg/dL, or a 24 hour creatinine clearance of <40 mL/min. (*Of note, this is a criteria for HRS in general, and not HRS type I*).
    - Absence of shock, uncontrolled bacterial infection, fluid loss, and treatment with nephrotoxic drugs.
    - No sustained improvement in renal function (decrease of SCr to ≤1.5mg/dL OR increase in creatinine clearance to ≥40 mL/min) after diuretic withdrawal and plasma volume expansion with 1.5L isotonic saline.
    - Proteinuria <500 mg per day (incorporating amendment 2 of topographic error)
    - Absence of granular casts on urinalysis
    - No ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

OT-0401 Exclusion criteria:

- Ongoing shock
- Uncontrolled (ongoing) bacterial infection
- Current fluid losses
- Acute liver disease due to factors known to be also directly nephrotoxic (e.g. acetaminophen overdose, mushroom poisoning)
- Confirmed pregnancy
- Severe cardiovascular disease as judged by investigator
- Evidence of intrinsic or parenchymal renal disease
- Current or recent treatment with nephrotoxic drugs, e.g. aminoglycosides or NSAIDS within 4 weeks

- Estimated life expectancy of less than 3 days

Reviewer comment: Severe respiratory illness, asthma and COPD were not among the exclusion criteria, in contrast to TAHRS.

Table 5. OT-0401 Pre-specified Study Timelines

Study Assessment	Pre-Study Period 14 +/-21[a] days	Active Study Period Day 0-14		Day 30 FU +/- 4 days	Day 60 FU +/- 10 days	Day 90 FU +/- 14 days	Day 180 FU +/- 25 days
		Day 1-13	Day 14 + (0-2) days				
SCr	X	X	X	X	X		
Need for Dialysis		X---------- →					
Transplantation		X---------- →					
Death		X---------- →					

Key Points on Study Timeline Specified by the Protocol
Screening Period:

- The protocol specified "approximately" one week of screening period to evaluate for the clinical diagnosis of HRS type I.

Reviewer comment:
Data demonstrated the pre-study period were 14 +/-21 days. The range of days between qualification and randomization were 0-14 days, the median (IQR) in days: terlipressin 0 (1), placebo 0 (2).

- In this pre-study period, "*baseline"* SCr measurement was defined as the latest non-missing SCr obtained BEFORE study medication administration.

14 Day Active Study Period:
[b]SCr is checked daily from Day 1 to Day 13 until one of the following:

- "Treatment Success" defined as SCr measurement of ≤ 1.5 mg/dL for *at least* 40 hours *at discretion of the investigator*
- Met criteria for dialysis or SCr level at Day 7 or later that was ≥ baseline value
- Liver transplantation
- Study withdrawal for other reasons (e.g. AE)
- Completion of 14 days of therapy

Reviewer comment:
Of those who stopped prematurely for AEs but were alive at Day 14 (6 in terlipressin, 2 in placebo arm), only one had a Day 14 SCr. Please see ***Error! Reference source not found.*** *for disposition.*

Day 14's window allowed for 2 additional days for SCr measurement, Day 14 + (0-2).

Reviewer comment:

Data showed four of the Day 14 SCr in the terlipressin arm were outside the pre-specified Day 14 + (0-2) window. Two of the four patients were counted as Treatment Success. According to the sponsor's pre-specified clinical and statistical protocol, treatment failure at day 14 was defined as the percentage of patients who experienced any of the following: SCr at or above baseline on day 7 or after, death, or met criteria for dialysis at any time during treatment. However, in the trial, patients were at times discontinued for "treatment failure" before Day 7 and/or with SCr slightly better than the baseline, particularly in placebo arm.

SCr follow up:
SCr was to be checked at for all patients on the Day 30 and 60 visits at investigational sites.

Study Medication Dosing Regimen:
Lysophilized terlipressin (with mannitol (b) (4)

- 1 mg (as a IV bolus over 2 minutes) every 6 hrs for up to 14 days,
- If after 3 days SCr is not reduced by ≥30% then increase to 2 mg every 6 hrs
- Discontinue 2 days after SCr ≤1.5mg/dL or after 14 days of therapy.
- Discontinue if SCr not decreased below baseline after 7 days or patient undergoes dialysis or liver transplant.

If dose limiting side effects occur, dosing should be stopped until adverse event is no longer severe and dosing could be re-started, at the discretion of the investigator, at 1 mg each 8-12 hours.

- If HRS recurs, terlipressin may be re-administered for those who had at least a partial response during the initial treatment course.

Placebo:
Lyophilized mannitol without the active ingredient terlipressin, given in the same dosing regimen as above.

Reviewer comment:
The above dosing regimen was at times not followed in the pivotal trial. For examples, patients were not up-titrated or had study treatments stopped earlier than specified in the protocol. Two patients, (b) (6), in terlipressin group received 0.5 mg, halved the initial starting dose, due to AEs of cyanosis and abdominal cramp, respectively.

Concomitant Medications
1) Recommended, but not required, concomitant medication for both treatment arms:

- Albumin to maintain serum albumin between 3.0 to 3.5 g/dL
- The following doses are recommended: 100 gram on day 1, 25 gram per day until the end of the study.

2) Prohibited Or Discouraged Medications:

- Diuretics-discouraged
- Vasopressive drugs
- Prostaglandin analogs

- Octreotide
- NSAIDs

Treatment, ancillary management:
Retreatment:
In the original protocol (section 5.1.3) patients who demonstrated at least a partial response during treatment course (a SCr concentration >1.5 mg/dL and more than a 50% reduction in SCr from baseline) and develop recurrence of HRS type I during the study or follow-up period, may be retreated with the initially assigned study drug for up to 14 days with a follow-up of at least 180 days for survival. Retreatment patients (n=2) were included in the safety but not efficacy analyses.

ANALYSIS
Pre-specified Primary Endpoint, Incidence of Treatment Success
Treatment success at Day 14 was defined as the percentage of patients alive who demonstrated a reversal of HRS (SCr ≤1.5 mg/dL on ≥2 measurements obtained 48 ± 8 h hours apart) without dialysis or recurrence of HRS.

Reviewer comments: Descriptions of the pre-specified and none pre-specified versions of the primary and secondary endpoints are located at the result's section.

Populations for Analysis:
ITT population:
All randomized patients who had at least one baseline assessment, except the retreated population for efficacy.

MITT population for the pre-specified primary analysis:
Unlike the ITT analysis population that includes all randomized, non-retreatment patients who had at least one baseline assessment, the pre-specified primary analysis, MITT, only includes patients who had not received liver transplant.

"MITT" population in Survival Analysis:
The ITT patients with either a missing transplant date or had a transplant date later than the date of the follow-up Visit Day being examined.

Missing Visit and Survival Data:
Per the sponsor's visit dates algorithm (dated August 31, 2006, 3 days after trial completion) "if the patient did not have a date for one of the visits and that visit date was needed for reference, the visit date was imputed" from the first dose date. "If a patient had an indication in the death dataset that they were still alive at a given visit, the date for that visit was obtained by adding x number of days minus one to the first dose date, where x was the day of the visit that was being imputed." In other words, this algorithm does not require verification against an actual death date. Lastly, the sponsor did not provide information on the incidence of missing telephone follow up visits.

Missing SCr Data from Dataset:
Not all SCr measurements recorded on CRFs are provided to reviewer for independent analysis. These data have been requested from the sponsor, but not all are available at the time of this review.

Handling of Missing Data:
Efficacy analyses:

- For treatment success at Day 14, missing data will be imputed as "not success."
- The Observed Case method will be used for survival, incidence and number of days on dialysis, and the repeated measures analysis.
- For all other efficacy parameters (HRS reversal), missing data will be replaced by the last available data point, including baseline.

OT-0401 Demographics:

Table 6. The Sponsor's Summary of Demographics and Baseline Characteristics (ITT)

Baseline Characteristics	Terlipressin (N=56)	Placebo (N=56)	Total (N=112) n (%)
Demographics			
Male (%)	41 (73.2)	39 (69.6)	80 (71.4)
Age (years), mean (SD)	50.6 (10.5)	52.9 (11.4)	51.8 (11.0)
Ethnic origin: White, n (%)	51 (91.1)	49 (87.5)	100 (89.3)
Disease characteristics			
Cirrhosis, n (%)	51 (91.1)	51 (91.1)	102 (91.1)
Cirrhosis due to alcohol	29 (51.8)	29 (51.8)	58 (51.8)
Cirrhosis due to hepatitis C	22 (39.3)	19 (33.9)	41 (36.6)
Ascites, n (%)	56 (100)	55 (98.2)	111 (99.1)
Grade 1	8 (14.3)	6 (10.9)	14 (12.6)
Grade 2	12 (21.4)	14 (25.5)	26 (23.4)
Grade 3	36 (64.3)	35 (63.6)	71 (64.0)
Child-Pugh Score, mean (SD)	11.7 (1.9)	11.2 (1.8)	11.4 (1.9)
Class A	0	1 (1.8)	1 (0.9)
Class B	9 (16.1)	10 (17.9)	19 (17.0)
Class C	43 (76.8)	44 (78.6)	87 (77.8)
MELD Score, mean (SD)	33.4 (6.0)	33.4 (6.3)	33.4 (6.2)
Alcoholic Hepatitis, n (%)	20 (35.7)	20 (35.7)	40 (35.7)
Clinical encephalopathy score, mean (SD)	1.5 (0.9)	1.3 (1.0)	1.4 (0.9)
Serum creatinine (mg/dL), mean (SD)	3.96 (2.19)	3.85 (1.17)	3.90 (1.75)
Patients with SCr >7.0 mg/dL, n (%)	6 (10.7)	0	6 (5.4)
Serum sodium (mmol/L), mean (SD)	130.6 (6.9)	132.4 (7.0)	131.47 (6.98)
Total bilirubin (mg/dL), mean (SD)	15.0 (13.6)	15.8 (15.1)	15.41 (14.29)
Precipitating Event for HRS			
Patients with a known precipitating factor, n (%)	30 (53.6)	31 (55.4)	61 (54.5)
Infection, n (%)	14 (25.0)	9 (16.1)	23 (20.5)
Gastrointestinal bleeding, n (%)	2 (3.6)	3 (5.4)	5 (4.5)
Diuretic treatment, n (%)	12 (21.4)	15 (26.8)	27 (24.1)
Large volume paracentesis, n (%)	5 (8.9)	4 (7.1)	9 (8.0)

Source: OT-0401 CSR/ Table 4.1.5, Table 4.1.6, Table 4.1.7, Table 4.1.8, Table 4.1.9

The sponsor's Table 7, module 2, 2.1.2.3

Reviewer Comments:

On average, the two groups are similar in baseline characteristics, including the mean baseline SCr, terlipressin 3.96 mg/dL and placebo 3.85 mg/dL. However, the distribution of SCr in terlipressin group was right skewed as compared to placebo, as reflected by the number of subjects with "baseline" SCr >7.0 mg/dL in terlipressin (n=6) than placebo (n=0) group. Of unclear reason, five of these six patients with "baseline" SCr >7.0 mg/dL were enrolled in the later half of the study.
Nonetheless, the median SCr, a measure of the average SCr that is less sensitive to the high-SCr outlier effect than the mean SCr, was in fact lower in terlipressin (3.3 mg/dL) than in placebo (3.8 mg/dL). This is because due to the right skewed distribution of the SCr in terlipressin group, there was also more patients with lower SCr (e.g. <4 mg/dL) in terlipressin than in the placebo group. The implication of this imbalance in the distributions of SCr on the overall mortality will be discussed later in section 0.

In trial OT-0401, a significant proportion of patients did not complete the 14 days study treatment period (80% terlipressin, 91% placebo). Of these patients, the reasons for discontinuation were difficult to validate for a number of reasons. The SCr outcome for terminating dosing in the clinical protocol (SCr ≥ baseline at Day 7 or later) was not followed by investigators. Many patients, particularly in the placebo group, were discontinued for "not much improvement in SCr" before Day 7. In addition, there are significant discrepancies between the sponsor's assessment of the reasons for ending study treatment and the reasons recorded on CRF by the investigators. According to the sponsor, the investigators were recording reasons for concluding the study treatment in an inconsistent manner for categories such as death, dialysis, and transition to palliative care, which were not specified on CRF. Hence, sponsor performed their own assessment in order to "standardize the investigator's response in a more systematic fashion". The sponsor's assessment was not pre-specified and it is unclear if it was blinded. Since reasons for discontinuation are not necessarily mutually exclusive, the choice of the primary reason for discontinuation is subject to bias, particularly if done in a retrospective, unblinded fashion. In the following table, the medical reviewer illustrates some of the discrepancies between the sponsor's assessment versus findings based on CRF or Division of Scientific Investigation (DSI) reports. The numbers in the table are based on medical reviewer's best assessment of the reason for discontinuation, taking together reports from investigator/CRF, DSI and the sponsor. The medical reviewer also tabulates the key "hard" clinical outcomes of non-completers.

Table 7. OT-0401 Study Populations and Disposition:

Subjects	**Terlipressin N (%)**	**Placebo N (%)**
Screened[a]	Unknown	Unknown
Randomized	56 (100)	56 (100)
Treated	56 (100)	55 (98)
Completed the 14 days of study treatment	11 (20)	5 (11)
Received less than 14 days of study treatment	45 (80)	50 (91)
Stopped for "Treatment Failure"	19	23
Stopped because of death	6	3
Stopped for hemodialysis	10[b]	7[d]

Subjects	**Terlipressin N (%)**	**Placebo N (%)**
Stopped for SCr not much improved	2 [c]	13
Stopped before Day 14 for Treatment Success	11	6
Stopped for transplant within Day 14	8	9
Early termination/Withdrawal:	7	12
Withdrawn due to adverse event	3 [e]	2
"Patient withdrew consent"	0	3
Physician decision/Administrative	1 [e]	1
Other:	3	6
Transition to palliative or comfort care	3 [e, f]	3 [f]
Withdrew against medical advice	0	2 [f]
Received contraindicated medication	0	1
Outcomes of non-completers [g]		
Received transplant within Day 14 [h]	8 (14)	11 [h] (20)
Received dialysis within Day 14	14 (25)	15 (27)
Death within 7 days	13 (23)	11 (20)
Death within 14 days	16 (29)	17 (30)
Stopped for TS still alive at Day 14	9 (82)	5 (100)
Retreatment w/ randomized study med [i]	1 (2)	1 (2)
Cross over to terlipressin	0 (0)	≥ 4 (7)

[a] the sponsor is not able to provide data.

[b] According to CRF documentation dated (b) (6) patient (b) (6) (terlipressin arm)'s study treatment on (b) (6) was stopped after only receiving a single dose because "patient (was) dialyzed". However, the sponsor disputes the start date for dialysis because on CRF of the 30-day follow-up, the initiation date of dialysis was (b) (6) [c] The sponsor counts this patient in the "stopped for SCr not improved" category.

[d] Patient (b) (6) (placebo arm) was not reported to have received dialysis. However, the sponsor reports in their analysis dataset that the subject received dialysis from (b) (6) (b) (4) found SAE report states that the patient declined dialysis based on religious reasons.

[e] The medical reviewer found 4 additional patients who could be counted as withdrawn due to AE. These patients were counted by the sponsor as transition to palliative care (b) (6) or physician decision (b) (6). To be objective, the medical reviewer did not count these additional cases based on her unblinded review in the above table.

[f] The investigators reported palliative care as the reason for concluding treatment for 3 patients in each treatment groups. The sponsor identified additional patients in both groups.

[g] Outcomes are not mutually exclusive.

[h] Two additional placebo patients, (b) (6) who did not stop study medication for transplant, but later received a transplant within Day 14. (b) (6) stopped for physician decision at Day 3 (SCr went from 3.1 to 4.1). (b) (6) did not receive study medication because of SBP discovered after randomization, and was transplanted on before Day 14 of supposed randomization date.

[i] An undisclosed number of patients in the placebo arm received open-labeled terlipressin therapy after discontinuing placebo therapy. The adverse events that occurred during the open-labeled terlipressin administration phase were attributed to placebo therapy. Retreatment and cross-over patients were included in the safety but not efficacy analyses.

Reviewer Comments: More subjects stopped for study treatment success on terlipressin (n=11) than placebo (n=5), and fewer stopped for SCr "not much improved" (terlipressin n=2 vs placebo n=13). However, this reduction in SCr on terlipressin did not translate into a reduction in the need for dialysis (terlipressin n=14, placebo n=15), an increase in the rate of liver transplantation (terlipressin n=8, placebo 11), or any reduction in mortality. The on-treatment death was higher in terlipressin (n=6) than placebo (n=3), as was death within Day 7 (terlipressin n=13, placebo n=11). Death within Day 14 was similar in terlipressin (n=16) as compared to placebo (n=17) group.

Only 17 subjects (15%) complete the full 14 day of study treatment. More completers are from the terlipressin group (n=11) than placebo (n=6). Nonetheless, the mean and median in length of treatment were not different between the two groups.

Lastly, patients who stopped study treatment for adverse events were lost to follow-up, e.g. terminated from the trial.

OT-0401-Analysis of OT-0401 Primary Endpoint(s)
The nominal effect in SCr should be viewed in light of the data issues discussed in review section 3.1 Submission Quality and Integrity .

Primary Endpoints
Pre-specified Primary Endpoint, Incidence of Treatment Success
Treatment success at Day 14 was defined as the percentage of patients alive who demonstrated a reversal of HRS (SCr ≤1.5 mg/dL on ≥2 measurements obtained 48 ± 8 h hours apart) without dialysis or recurrence of HRS.
The recurrence of HRS was defined in August 31, 2006's statistical plan (Appendix 8.1.17) as any SCr measurement of >2.5 mg/dL after the initial SCr ≤1.5 mg/dL. To confirm that there was not recurrence within the pre-specified 14 day treatment window, one had to have a Day 14 SCr measurement in order to be counted as treatment success.

Pre-specified primary analysis was the MITT analysis. Unlike the ITT analysis population that includes all randomized, non-retreatment patients who had at least one baseline assessment, the pre-specified primary analysis, MITT, only includes patients who had not received liver transplant.

Table 8. Pre-specified Primary Endpoint, Incidence of Treatment Success, OT-0401

Terlipressin	Placebo Control	P value
14/56 (25%)	7/56 (12.5%)	0.093 [a] ITT
14/48 (29%)	7/44 (16%)	0.131 [a, b] MITT

[a] Analysis by CMH test for general association adjusted for AH.
[b] The Modified intention to treat (MITT) population, excludes patients who received a liver transplant prior to Day 14 from the denominator.

Reviewer Comment: Compared to placebo, the terlipressin group had a lean toward higher incidence of treatment success at Day 14, but this lean did not reach statistical significance. This lean toward treatment success with terlipressin as compared to placebo was true across AH stratum (data not shown); this is expected, as the randomization was stratified by AH.

From the first day of achieving "Treatment Success", the decision whether to continue treating with study medication and monitoring SCr to Day 14 was left to investigators' discretion. The medical reviewer explored whether there is systematic difference in the length of treatment and SCr monitoring after achieving treatment success (**Table 9**).

Table 9. Additional Days of Therapy with Study Medication After the Initial SCr ≤1.5mg/dL

TRT	Subjects with SCr Values Less or Equal to 1.5mg/dL On Study Medication Treatment (n)	Additional Days of Treatment Mean +/- Std Dev	Additional Days of Treatment Median (IQR)
Terlipressin	19	5.1 +/- 4.2	3.1 (12.0)
Placebo	8	4.0 +/- 3.3	2.4 (8.7)

For this analysis, the time to a successful SCr was defined by having a SCr value ≤1.5mg/dL independent of dialysis or transplantation. Additional days of therapy was determined by subtracting the date and time of the last non-retreatment dose to that of the first successful SCr measurement.

On the whole, the terlipressin group appears to have longer treatment and more SCr values obtained after the first SCr became ≤1.5mg/dL. These small differences in treatment and SCr monitoring affect the interpretation of the observed difference in the delta SCr between the two treatment arms over the duration of the study period (e.g. Repeated Measures Analysis of Change from Study *Day 1* to Day 14 SCr Values, [**Table 12**]).

Alternative Primary Endpoint Defined After Trial Completion

Table 10. Reversal of HRS on Treatment (one or more SCr at or below 1.5 mg/dL)- An Endpoint Defined After Data Collection

Sponsor's HRS Reversal was defined as having "any SCr values *before* the last non-missing dose date in a patient who had not had a transplant or dialysis, less than or equal to 1.5 mg/dL" (Statistical Algorithm Amendment One, Appendix 8.1.17).

	Terlipressin n/N (%)	Placebo Control n/N (%)	P value **95% CI**
Sponsor ITT	19/56 (34%)	7/56 (13%)	0.008[a]
FDA ITT	17/56 (30%)	8/56 (14%)	0.068[b]
MITT	17/48 (35%)	7/44 (16%)	0.060[c]

[a]Sponsor's analysis by CMH test for general association adjusted for AH using the ITT population.
[b, c] FDA analysis by 2-tailed Fisher exact test.

Reviewer Comment: According the sponsor's definition and analysis of HRS reversal, the terlipressin group appears to have a statistically significant increased incidence of HRS reversal compared with that of the placebo group. The reviewers are not confident about the clinical significance of this finding for the following reasons.

1) HRS reversal, unlike the pre-specified treatment success endpoint, included subjects with non-sustained improvement in SCr to less than 1.5 mg/dL. Furthermore, the sponsor counted patients as HRS reversal despite subsequent HRS recurrence. It is unclear if a one-time reduction in SCr that then goes away constitutes renal preservation, a position FDA has consistently expressed.

2) *We can not determine if blinding was preserved when the sponsor defined the HRS reversal endpoint. In the pivotal trial, the last patient was enrolled on* (b) (6) *and therefore, the 14-Day study treatment data collection for the primary endpoint was completed by* (b) (6)

3) The p values by FDA analyses are not statistically significant. FDA's ITT analysis counted one more placebo patient with HRS reversal. This is because a placebo subject (b) (6) *with a SCr value of 1.5 mg/dL obtained while on study treatment and prior to liver transplantation was excluded for receiving a liver transplant subsequently on the date of SCr measurement. FDA analyses had two fewer terlipressin subjects counted as HRS reversal because they either died or had HRS recurrence within the 14-day study period. Subject* (b) (6) *subsequently died before the 14-day end of active study period. Subject* (b) (6) *had a HRS recurrence (SCr 2.8 on Day 11) during the 14-day active study period.*

OT-0401: Analysis of the Five Pre-specified Secondary Endpoints in the Pre-specified Order

In the original protocol, finalized on March 25, 2004, the five secondary endpoints were to be done "in a nested sequential way." The results of the 5 pre-specified secondary endpoints presented below should be viewed in that context; since the pre-specified primary endpoint failed to meet statistical significance, the secondary endpoints can arguably be viewed as "exploratory" in nature.

Secondary Endpoint #1:

- Pre-specified:

Change from *baseline* to Day 14 in renal function (mean SCr) by "an analysis of variance model with treatment and AH strata as covariates" (ANCOVA model).

Please see Table 11 below for the result of the FDA analysis based on pre-specified analysis plan. The analysis population is the patients who did not receive dialysis or transplant and had Day 14 SCr measurements provided in the SCr dataset dated August 2008.

- Subsequent Change to Secondary Endpoint #1, found during review:
  Change from *Day 1* to Day 14 of SCr values, *regardless of dialysis or transplantation status*, by *Repeated Measure Analysis (see* Table 12 *below)*

*Reviewer Comments**:** the sponsor did not formally amend or notify FDA of the change in this pre-specified SCr analysis. The change was noted during review.*

Table 11. Change from Baseline to Day 14 in Renal Function (Mean SCr) Analyzed by Using An Analysis of Variance Model with Treatment and AH strata as Covariates (FDA analysis)

	Terlipressin (n=23)	Placebo (n=14)	P value
Mean +/- standard deviation)	-1.59 +/-1.22	-1.45+/-0.99	0.74[a]
Median (IQR)	-1.50 (1.11)	-1.60 (1.41)	0.81[b]

[a] Two sample t-test
[b] Wilcoxon test

In the above FDA analysis, the average reductions in SCr from Day 0 to Day 14 were similar between terlipressin vs placebo group.

The FDA analyses of this secondary endpoint differ from the sponsor's analysis below (**Table 12**). The sponsor's analysis is in place of the pre-specified analysis.

Table 12. The Sponsor's Repeated Measures Analysis of Change from Study *Day 1* to Day 14 SCr Values *Regardless of Transplant or Dialysis Status*

Time Point	Terlipressin N	Terlipressin LS Mean (SE)	Placebo N	Placebo LS Mean (SE)	Terlipressin vs. Placebo LS Mean[a] (SE)	P-value[b]
Day 1	51	0.1 (0.20)	51	0.3 (0.20)	-0.2 (0.28)	0.466
Day 2	48	0.0 (0.20)	49	0.3 (0.20)	-0.3 (0.28)	0.230
Day 3	39	-0.2 (0.21)	42	0.3 (0.21)	-0.5 (0.29)	0.082
Day 4	34	-0.4 (0.22)	36	0.3 (0.21)	-0.7 (0.30)	0.018
Day 5	30	-0.8 (0.22)	33	0.4 (0.22)	-1.1 (0.30)	<0.001
Day 6	24	-0.8 (0.23)	28	0.3 (0.22)	-1.1 (0.32)	<0.001
Day 7	22	-1.0 (0.24)	23	0.4 (0.23)	-1.4 (0.33)	<0.001
Day 8	19	-1.0 (0.25)	13	0.2 (0.27)	-1.1 (0.36)	0.002
Day 9	18	-0.8 (0.25)	9	-0.1 (0.30)	-0.7 (0.39)	0.071
Day 10	17	-1.0 (0.25)	7	-0.4 (0.33)	-0.5 (0.41)	0.203
Day 11	14	-0.8 (0.26)	6	-0.4 (0.35)	-0.4 (0.43)	0.409
Day 12	12	-0.9 (0.28)	6	-0.5 (0.35)	-0.4 (0.44)	0.307
Day 13	12	-0.9 (0.28)	6	-0.5 (0.35)	-0.4 (0.44)	0.350
Day 14	38	-1.0 (0.21)	33	-0.4 (0.21)	-0.6 (0.30)	0.055
Overall P-value		**-0.7 (0.19) <0.001**		**0.0 (0.19) 0.956**	**-0.7 (0.26)**	**0.009**

a: Calculated as the terlipressin LS Mean Change from baseline minus placebo LS Mean change from baseline.
b: From Repeated Measures ANOVA as implemented in Proc Mixed with factors Treatment, Day, Baseline Strata (alcoholic hepatitis present or not), Treatment by Day, and Repeated statement with factor Patient nested in Strata. Treatment p-values within Day are obtained from the Treatment by Day interaction, whereas the overall treatment p-value is obtained from the overall treatment comparison.
Note: Model uses compound symmetry covariance matrix and maximum likelihood estimation.
Cross Reference: Data Listings 10.1, 25, and 27

(Section 5.3.5.1, CSR OT-0401, Table 4.2.7)

Reviewer Comments:
According the submitted analyses of the five secondary endpoints, this is the only secondary endpoint that "succeeded". The sponsor' analysis shows a small (-0.7 mg/dL), but statistically significant (P=0.009), change in SCr between the two treatment groups. This submitted analysis is not pre-specified and does not demonstrate convincing clinical significance for the following reasons.
1) In the sponsor's analysis, the Day 14 values included patients who received dialysis or transplantation before Day 14. Transplantation and dialysis are definitive non-pharmacologic treatments for HRS and renal failure, respectively, and SCr values obtained after transplantation and dialysis reflect, to a large extent, the effectiveness of these interventions. Furthermore, of the 71 Day-14 SCr values used in the sponsor's analysis, only 38 values are pre-dialysis and pre-transplantation (see Table 13*). Therefore, the Day 14 SCr values, as used by the sponsor in the analysis, do not reliably measure the terlipressin effect on SCr.*
2) The submitted repeated measures analysis compares the changes in SCr from "baseline" at multiple time points between the two treatment groups. It is sensitive to small differences in the number of time points after achieving treatment success between the two treatment arms.
3) This analysis is sensitive to the definition of baseline SCr, which is not uniformly defined.

Table 13. A Comparison of the Number of SCr Measurements in Respective Treatment Day in Sponsor vs. FDA Analyses

Study Day	Sponsor table 4.2.7 (N)	FDA Analysis (N)
0	112	111
1	102	101
2	97	92
3	81	80
4	70	69
5	63	62
6	52	51
7	45	45
8	32	32
9	27	27
10	24	23
11	20	20
12	18	18
13	18	18
14	71	38

Reviewer Comment: All patients who remained in the trial were to have SCr measured at Day 14. However, only the SCr measurements obtained before dialysis and transplantation accurately reflect the study treatment effect.
While both analyses were based on the sponsor's dataset SCr, the FDA analysis excluded SCr measurements obtained after liver transplant or initiation of dialysis, and therefore account for the differences in the number of SCr values used in the FDA vs. the sponsor's analyses throughout the 14 day period.

Secondary Endpoint #2: Incidence of Treatment Failure

The incidence of treatment failure at Day 14, defined as the percentage of patients who had SCr ≥ baseline after Day 7, died, or fulfilled the criteria for dialysis at any time during treatment.

Table 14. The sponsor's Summary of Incidence of Treatment Failure at Day 14 using Last Observation Carried Forward

Population / Outcome	Terlipressin N n (%)	Placebo N n (%)	P-value[a]
MITT at Day 14	N=48	N=44	
Treatment Failure	27 (56.3)	29 (65.9)	0.339
Reasons for Treatment Failure at Day 14[b]			
Death	16 (33.3)	17 (38.6)	
Met Criteria for Dialysis	12 (25.0)	10 (22.7)	
SCr ≥ Baseline after Day 7	21 (43.8)	27 (61.4)	
ITT	N=56	N=56	
Treatment Failure	31 (55.4)	37 (66.1)	0.247
Reasons for Treatment Failure at Day 14[b]			
Death	16 (28.6)	17 (30.4)	
Met Criteria for Dialysis	15 (26.8)	16 (28.6)	
SCr ≥ Baseline after Day 7	24 (42.9)	34 (60.7)	
a: From a CMH test for general association adjusted for baseline strata (alcoholic hepatitis present or not).			
b: Patients may be counted for more than one reason.			
Cross Reference: Data Listings 10.1, 19, 21.1, and 25			

(Section 5.3.5.1, CSR OT-0401, Table 4.2.9)

Reviewers' Comments: "Treatment failure" does not include subjects who received simultaneous liver-kidney transplant for HRS. There is no statistically significant difference in treatment failure between the two treatment groups. In addition, the validity of the sponsor's result is limited by the lack of a uniform definition of baseline SCr as discussed earlier.

Secondary Endpoint #3: Incidence of At Least Partial Response at Day 14

- Incidence of Partial Response ***at*** Day 14 was defined as the percentage of patients with SCr above 1.5 mg/dL, but more than a 50% reduction from *baseline*.
- Protocol Amendment No. 2 (September 12, 2005)
  Harmonized the definition of Incidence of Partial Response ***at*** Day 14 with that of Treatment Success ***at*** Day 14 in order to combine the two into **"**The Incidence of Achieving At Least a Partial Response". Therefore, the amended secondary endpoint was defined by the sponsor as the percentage of patients with a more than a 50% reduction from *baseline, regardless of whether the absolute value is 1.5 mg/dL*.

We performed this analysis according to the sponsor's pre-specified statistically analysis plan (see Table 15). The sponsor's submitted analysis, Incidence of Partial Response **through** Day 14, is also included for comparison.

Table 15. OT-0401 secondary endpoints #3

	Terlipressin n (%)	**Placebo n (%)**	**P-value**
FDA analysis			
MITT	N=48	N=44	
Treatment Success	14 (29)	7 (16)	
Partial Response **at** Day 14	1 (2)	2 (5)	0.2165
Treatment Success or Partial Response	14 (29)	8(18)	
Sponsor analysis			
MITT	N=48	N=44	
Treatment Success	14 (29)	7 (16)	
[a]Partial Response **through** Day 14	7 (15)	4 (9)	0.096
Treatment Success or Partial Response	16 (33)	8 (18)	

[a]Partial Response **through** Day 14, the submitted result by the sponsor. No change to the pre-specified statistical analysis plan was submitted.

In either analysis, there is no statistically significant difference in Combined Incidence of Treatment Success and Partial Response between the two treatment groups. Partial response at Day 14 in the prespecified analysis only counts SCr of interest at Day 14. Partial response through Day 14 in the sponsor's analysis counts all patients with any one SCr that meet the criterion from Day 1 to Day 14.
As shown in the above table, the number of subjects with "Treatment Success" plus the number with "Partial Response" exceeded the number of subjects with "Treatment Success or Partial Response". This is because a person can be counted both as a "Treatment Success" and "Partial Response".

Secondary Endpoint #4: Transplant-free Survival up to day 180 (ITT)
The sponsor defined "transplant-free survival" up to day 180 as the time (in days) that each patient survives without undergoing a liver transplant from the beginning of the study until the 180-day follow-up point. If a patient has a liver transplant or otherwise drops out of the study prior to the 180-day follow-up point, he will be censored at that time. The sponsor refers to this analysis as the modified intention to treat analysis, MITT. We believe this analysis is more accurately named as the transplant-free survival ITT analysis because the analysis population is the ITT population. The only difference from the overall survival ITT analysis is that in this analysis the patients are censored at the time of transplant.
Please see analyses Table 18 and Figure 2 in safety section for results and discussion.

Secondary Endpoint #5: Overall Survival up to day 180 (ITT).
Overall survival (ITT) up to Day 180, defined as the time (in days) that each patient survives whether or not a liver transplant was performed. If a patient drops out of the study prior to the 180-Day follow-up, he/she will be censored at that time.
Please see analyses Table 18 and Figure 1 in safety section for results and discussion.

Other Endpoints

Table 16. The mean change from baseline through Day 14 in MELD score

Study	Terlipressin n LSMean (SE)	Control n LSMean (SE)	P value
OT-0401	25 -4.4 (0.92)	18 -2.2 (1.06)	0.008*

[a]Repeated measures analysis with factors for treatment, day, treatment by day interaction, AH strata, and patient nested within AH strata. This analysis used the ITT population. Source: Table 4.3.83 of study report.

This analysis is one of the tertiary endpoints, evaluating the change from baseline in MELD score at the following 5 time points: day 3, 7, 14 or end of study drug administration, 30 and 60. There appears to be a statistically significant improvement in MELD score from baseline to Day 14. However, the sponsor did not provide a dataset to allow independent derivation of the MELD score (datasets did not include etiology of liver disease and laboratory values for timed MELD score derivations were not necessarily from the same date).

SAFETY OUTCOMES:

DEATH:

1. On-Treatment Death

Given the short half-life of IV terlipressin, incidence of death on-treatment was evaluated to avoid any dilution of safety signal with increasing time off-treatment. The sponsor's summary of on-treatment deaths are summarized in Table 17, where "on-treatment death" was simply defined as death "during the period of study drug administration," without specifying the time window between the last dose and death.

Table 17. The Sponsor's Summary of On-Treatment Deaths in OT-0401

Tx Group/ Pt ID	Age/ Gender	Cause of Death (Adverse Event Verbatim)	Study Day of Death	Baseline SCr (mg/dL)	Baseline MELD/ Child-Pugh Score	Baseline Total Bilirubin (mg/dL) / Serum Sodium (mmol/L)
Terlipressin						
(b) (6)		Sepsis	5	3.9	40 / 14	32.4 / 130
		Hepatic insufficiency	2	9.8	40 / 15	39.2 / 119
		Hepatic insufficiency	2	7.6	ND	35.0 / 123
		Hepatic insufficiency	2	11.9	ND	11.7 / 117
		Hepatic insufficiency	2	3.32	39 / 14	18.3 / 126
		Hepatic insufficiency	1	5.3	40 / 13	35.3 / 134
Placebo						
(b) (6)		Overwhelming sepsis Refractory hepatorenal syndrome	4	4.2	35 / 10	2.9 / ND
		Esophageal variceal hemorrhage	3	2.03	19 / 11	ND / 130
		Hepatic insufficiency	2	5.56	40 / 12	28.0 / 134

Tx = treatment; Pt ID = patient identification number; SCr = serum creatinine; M = male; F = female; ND = not determined.
Note: 4 of the 6 patients in the terlipressin group and 1 of the 3 patients in the placebo group had alcoholic hepatitis.
Note: (b) (6)
a: High dose – one or more individual doses was at least 2 mg.
Source: OT-0401 CSR / Table 4.3.15 and Appendices 8.2.29 and .8.2.26

According to the table above, the incidence of on-treatment death was twice as high in terlipressin (6) vs. control group (3). Seven of the nine deaths "on-treatment" (5 terlipressin patients, 2 placebo patients) occurred at (b) (6)

The sponsor has argued that the higher death rate in the terlipressin group was due to sicker patients enrolled in the terlipressin group evident by the higher "baseline" total bilirubin and lower serum sodium. However, given the above mentioned problems with baseline laboratory values, it is difficult to draw that conclusion convincingly. The medical reviewer believes that the relationship of terlipressin and on treatment death needs to be further explored in an additional randomized, controlled, and double-blinded study before terlipressin registration.

The sponsor's definition of on-treatment death would exclude subjects who died just after "study treatment termination" even when the death occurs shortly after the last dose of study medication. As such, this medical reviewer explored the incidence of on-treatment death defined by having the same death and the last dose date. According to this medical reviewer's analysis, the number of on-treatment deaths was 8 in terlipressin and 6 in placebo group, respectively, and therefore, does not appear to be a significant on-treatment death signal. However, since the

sponsor's dataset provided only date but not time of death, this result is limited by the extent of the information.

2. 180 Day All-Cause Mortality

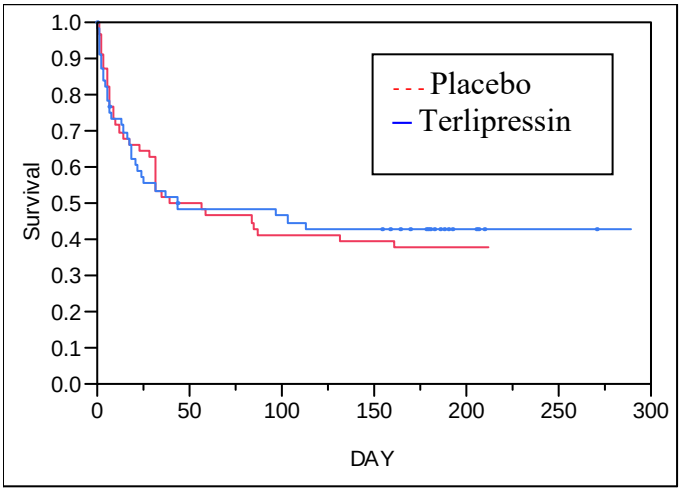
Table 18. 180-Day Overall and Transplant-free Survival in Study OT-0401

180-Day Survivals	Terlipressin N=56 n (%)[3]	Placebo Control N=56 n (%)[3]	P value
Overall Survival[1]	24 (43%)	21 (38%)	P=0.84, By ITT[a]
Transplant-free Survival[2]	6 (27%)	5 (18%)	P=0.771 By ITT[a]

[a]Analysis using a logrank test stratified by AH. ITT population.
[1]Includes patients without a known death on or before the specified time point.
[2] The sponsor's transplant-free survival included any subjects who were not known to be dead or transplanted at Day 180 (e.g. patients who were lost to follow-up or had unclear transplant status could be included).
[3] The percentages are calculated using product limit estimates.

Reviewers' Comments: The sponsor censored patients at the time of transplant in the "transplant-free" survival analysis. This means when a subject underwent a transplant and subsequently died within 180 days of randomization, this subject was censored rather than counted as having a death event. Per the sponsor's analyses and confirmed by reviewers, the 180 Day survivals were similar between the two treatment arms. Of note, for those who did not receive liver transplantation by Day 180, 6 and 5 were alive on terlipressin vs placebo, respectively. The 180 Day overall and "transplant-free" survivals are also summary in the following Kaplan-Meier plots Figure 1 and Figure 2, respectively.

Figure 1: The Sponsor's Overall 180 Day Survival



Reviewers' Comment: In Figure 2, the duration of follow-up for survival appears somewhat different between the two groups. To mitigate the potential bias introduced in the uneven follow-

up, an analysis was then performed by identifying all the subjects whose Day of last follow up was less than 180 Day and assigning them death status on Day 180. In doing so, the p value was not significantly different (data not shown).

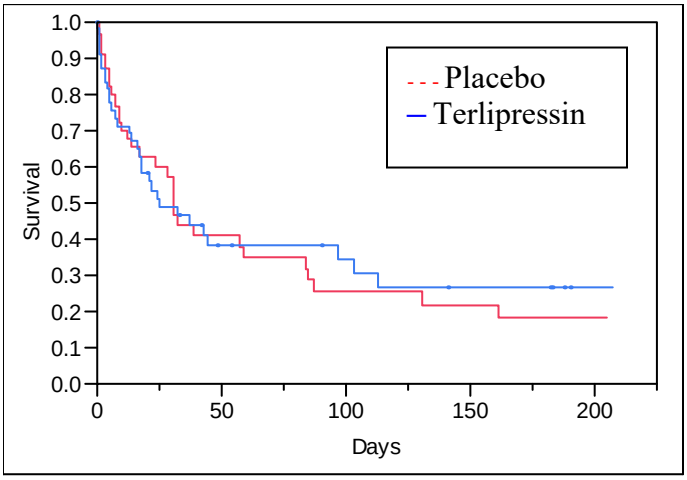
Table 19. FDA Analysis: Cumulative Incidence of Overall Death and At Risk of Events by Excluding the Subjects Who Were Lost to Follow-up As Alive

N	Day 14	Day 30	Day 60	Day 90	Day 180
Terlipressin					
Death	16	25	29	29	32
At risk[1]	40	31	27	27	19
Placebo					
Death	17	21	30	33	35
At risk	39	35	26	23	14
P values[2]	0.93	0.45	0.96	0.73	0.84

[1] At risk population includes only patients are known to be alive at Day 180. Excluded are 5 patients who are lost to follow-up at Day 180. This is different from the sponsor's analysis (Table 18) which counted the lost to follow-up as alive. The p-value, however, is the same as the sponsor's.
[2] P values are generated from the stratified log rank test.

As shown in Figure 1 and Table 19, overall survival up to the 180 Day visit is similar in the two treatment arms.

Figure 3. 180 Day Survival (ITT Population before Transplant)



Kaplan Meier's time to event curve, with event defined as death and subjects are censored for transplant (the sponsor's definition). Subjects were also censored if they didn't have transplant and didn't die on the last date of follow-up.

A similar pattern is seen between 180-day survival before transplant and overall 180-day survival, thus ruling out the effect of differential transplantation rate between the two groups driving the survival.

Other analysis performed by the reviewers:

In response to the sponsor's argument that the overall lack of mortality benefit observed in the trial was due to an imbalance in the baseline SCr at an arbitrary cut-off of >7 mg/dL, the reviewers performed additional analysis. We explored a proportional hazards model to adjust for baseline SCr differences between the groups. We also included terms for age and alcoholic hepatitis (AH) status which were likely to affect survival. After adjusting for baseline SCr, we still did not see a significant effect of terlipressin treatment on survival (p of 0.8095). Based on this analysis, we do not believe that one can assert the overall lack of mortality benefit observed in the trial was due to an imbalance in the baseline SCr.

Analyses of the time to event split by the median randomization date, 8/28/2005, showed similar results for the first and second halves of the trial.

Please see Appendices for the narratives on all cause-death up to the 180-Day visit and on "severe" adverse events up to 30 days post treatment termination.

Dropouts and/or Discontinuations

For the breakdown of the early termination, please see **Table 7**, Table 20 summarizes the AEs that contributed to dose withdrawal, interruption, or reduction.

Table 20. Adverse Events Leading to Withdrawal, Interruption, or Dose Reduction of Randomized Study Treatment OT-0401

Adverse Events	**Terlipressin (n = 8)** SUBJID	**Placebo (n = 2)** SUBJID
Pain in extremity, Vaginal hemorrhage Conjunctival hemorrhage, Pain in extremity	(b) (6)	
Depressed level of consciousness		
Pulmonary hemorrhage		
Cyanosis of fingers and toes		
Respiratory failure/pulmonary edema/ hypoxic[2] respiratory distress		(b) (6)
Livedo reticularis[3]		
Mottling of both lower extremities		
Myocardial infarction		
Enterococcal sepsis		
Hypotension (requiring pressor)		(b) (6)
Abdominal Cramp		

[1] (b) (6) (terlipressin): This patient had "intense bilateral thigh pain", "increased confusion", "non-serious right subconjunctival hemorrhage", "slight vaginal bleeding", and apparently worsening hepatic labs. In the medical reviewer's opinion, these AEs could have contributed to the transition to comfort care only.
[2] (b) (6) developed alveolar hemorrhage, an AE not included in the original submitted AE dataset.
[3] (b) (6) developed burning leg pain on terlipressin, an AE not included in the original submitted AE dataset

Significant Adverse Events

OT-0401:
Death- see Table 19 and Figure 2 above.

Treatment-Emergent Adverse Events Other than Death:
Non-fatal treatment-emergent adverse events (TEAEs) occurred more frequently in subjects of the terlipressin than placebo group.

Table 21. "Treatment Emergent" AEs that occurred 30 days post treatment termination

Treatment	Subjects (n)	TEAE (n)
Placebo	51	214
Terlipressin	53	277

Used the Sponsor's AEDOSE Dataset but with inclusion of only the TEAE that occurred 30 days post treatment termination, as defined by the sponsor.

The number of subjects who experienced TEAEs was similar in the two treatment groups (placebo [51] vs. terlipressin [53]). The numbers of TEAEs by counting each TEAE regardless of recurrence were more in terlipressin (277) than placebo (214) group. When counting the recurrent TEAEs only once per subject, the incidence of TEAE were also higher in terlipressin (203) than placebo (264) group

As the duration of follow-up for TEAE, 30 days post treatment termination, was defined nearly one year after trial commencement, the medical reviewer examined the lengths of follow-up for AE in the two treatment groups (see **Table 22** below).

Table 22. The Length of Follow-up to the Emergence of AEs Post Treatment Termination in Sponsor's AEDOSE dataset

Treatment	Median (IQR) Days	Maximum Days
Placebo	1.0 (7.0)	136
Terlipressin	1.0 (5.0)	30

The number of day post treatment termination is calculated by subtracting the last treatment date from the start date of the AE then plus one.

The medians and IQRs of the length of follow-up to the emergence of AEs post treatment were similar between the two treatment arms. However, there were four subjects in placebo group who did not adhere to the sponsor's specified follow up period for identifying TEAE: (b) (6)

who developed "hepatic failure" 135 days post treatment termination, (b) (6) who had "unknown cause for death" at 44 days post treatment termination, (b) (6) who developed "hypomagnesemia" 36 days post treatment termination, and (b) (6) who developed "renal failure" at 31 days post treatment termination. No subject in the terlipressin arm was followed for TEAE beyond 30 days.

Of the TEAEs, the AEs that occur more frequently in terlipressin than placebo group are summarized in Table 23. Adverse events that occur in greater than 10% of the subjects in terlipressin group are in bold text. Results presented below are based on the analyses were performed using AEDOSE dataset provided by the sponsor.

Table 23. Treatment Emergent Adverse Events that Occur More Frequently in Terlipressin than Placebo Group

MeDRA Preferred Term	**Terlipressin (N= 56) n (%)**	**Placebo (N=55) n (%)**
Respiratory Symptoms	19 (34%)	9 (16%)
Dyspnea	5	3
Bronchospasm and Wheeze	6 (11%)	0 (0%)
Respiratory failure	3	2
Respiratory distress	2	3
Acute respiratory distress syndrome	1	1
Hypoventilation	1	0
Respiratory acidosis	1	0
Cardiac Symptoms	15 (27%)	9 (16%)
Arrhythmia	10 (18%)	9 (16%)
Atrial fibrillation or flutter	5	4
Arrhythmia (type not otherwise specified by the sponsor)	0	1
Supraventricular tachycardia	3	2
Supraventricular extrasystole	1	1
Ventricular fibrillation	0	1
Ventricular tachycardia	1	0
Other Cardiac Events	5 (9%)	0 (0%)
Right ventricular failure	1[1]	0
Cardiac Arrest	2	0
T wave changes	1	0
Myocardial Infarct	1	0
Gastrointestinal Symptoms	25 (45%)	15(27%)
Abdominal pain	7 (13%)	4 (7%)
Vomiting	9 (16%)	2 (4%)
Nausea	9 (16%)	9 (16%)

MeDRA Preferred Term	Terlipressin (N= 56) n (%)	Placebo (N=55) n (%)
Probable Ischemic Events	7 (13%)	2 (4%)
Cyanosis	1	0
Livedo reticularis	1	0
Abdominal Pain with GI bleed	1	0
Extremity pain[2]	3	0
Chest pain or tightness	1	2
Others:		
Headache	4	2

[1]Subject (b) (6) developed the right ventricular failure 2 days into the open-label treatment with terlipressin, and 4 days following therapy with placebo. In the sponsor's AE dataset, right ventricular failure was attributed to placebo therapy. The medical reviewer disagrees with the sponsor's attribution. I believe right ventricular failure is more appropriately attributed to terlipressin use than placebo while I acknowledge that the recent use of placebo could be a potential confounder.
[2]Subject (b) (6) was found to have extremity pain on terlipressin in CSR, CRF indicate that terlipressin was discontinued due to AE, but this AE was not in AE dataset.

The vasopressin analogue, DDAVP, is thought to raise vWF levels and promote primary hemostasis; vasopressin has been used to treat acute esophageal hemorrhage in portal hypertension. Therefore, the medical reviewer evaluated the hematologic adverse event profile for terlipressin. The medical reviewer found higher incidence of total bleeding with terlipressin than placebo in the liver disease population. This finding appears paradoxical. While the increased incidence of bleeding with terlipressin might be related to chance alone, potential effect(s) of terlipressin on other hematologic or coagulation parameters can not be ruled out. In OT-0401, basic hematologic parameters, such as CBC, were not available for review. In TAHRS, a case of pancytopenia with terlipressin was reported, and hemorrhagic treatment emergent adverse events were slightly higher in terlipressin (patient [n=6], event [n=7]) versus placebo (patient [n=3], event [n=3]).

Table 24. Bleeding Adverse Events

MeDRA Preferred Term	Terlipressin (N= 56) n (%)	Placebo (N=55) n (%)
Any Bleeding or Hemorrhage	**22** (39%)	**9** (16%)
Conjunctival hemorrhage	1	0
Epistaxis	3	1
Gingival bleeding	1	0
Guaiac Positive Stool	1	0
Intracranial Hemorrhage	0	1
Haematochezia	1	1
Hematuria	1	0
Haemorrhoidal hemorrhage	2	0

MeDRA Preferred Term	Terlipressin (N= 56) n (%)	Placebo (N=55) n (%)
Hempotysis[1]	1	0
Haematuria	1	0
Intra-abdominal hemorrhage[2]	1	0
Melena	0	2
Mouth hemorrhage	1	0
Oesophageal varices hemorrhage	2	2
Operative hemorrhage	1	1
Peritoneal hemorrhage[3]	1	0
Pulmonary alveolar hemorrhage	1	0
Pulmonary hemorrhage date unknown[4]	1	0
Rectal hemorrhage	1	0
Upper gastrointestinal hemorrhage	0	1
Vaginal hemorrhage	1	0

[1]According to CRF, subject (b) (6) developed hemoptysis on terlipressin and pulmonary hemorrhage was suspected. Neither hemoptysis or pulmonary hemorrhage was not noted in the sponsor' AE dataset. When asked to comment, the sponsor responded that since pulmonary hemorrhage was only suspected and not an established cause, this adverse event was instead coded as acute respiratory distress syndrome.
[2] (b) (6) was originally assigned to placebo therapy, but developed intra-abdominal hemorrhage during the later open-labeled terlipressin phase of the therapy.
[3] (b) (6) was originally assigned to placebo therapy, but developed peritoneal hemorrhage during the later open-labeled terlipressin phase of the therapy.
[4] Subject (b) (6) was noted in CRF to have biopsy proven pulmonary hemorrhage, date of which was not provided. This was not in AE dataset. The sponsor is unable to provide the date of the biopsy.

Laboratory Results:

The sponsor provided laboratory data on chemistry (excluding serum magnesium) and liver function panel. The sponsor did not provide any routine hematologic parameters (e.g. CBC) for analysis. The changes from "baseline" to Day 14 in laboratory parameters for subjects with non-missing data for both days are calculated. These changes characterized below.

Table 25. The Change in Total Bilirubin, Day 14 minus Day 0:

	Terlipressin n=36 (64%)	Placebo n=31 (55%)
Mean+/-Std Dev (mg/dL)	-2.4 +/- 9.7	-1.5 +/- 10.3
Median (IQR) (mg/dL)	-0.5 (4.1)	-0.9 (4.4)

While the distribution for the delta total bilirubin was parametric for placebo group, it was non-parametric for the terlipressin group. As such, both the main and median values are presented. Compared to the terlipressin group, placebo therapy appears to have a larger decrease in total bilirubin from Day 0 to Day 14. However, the intra-group variabilities were large as compared to the magnitude of the change.

Table 26. The Change in INR, Day 14 minus Day 0:

	Terlipressin n=27 (48%)	**Placebo n=21 (38%)**
Mean+/-Std Dev	0.06 +/- 0.4	0.3 +/- 1.1
Median (IQR)	0.1 (5.9)	-0.04 (5.2)

Overall, the delta INR **Day 14 minus "Day 0"** values were minimally changed in either group. In the placebo group, the distribution of the change in INR was nonparametric, with one outlier ((b) (6) (b) (6) who had a significant increase in INR of 4.5 (from 1.75 to 6.25). The median INR from relative Day "0" to Day 14 was a slight decreased in placebo group (-0.04), but a slight increase in the terlipressin group (0.1); these small changes in median INR were in the setting of relatively large amounts of intra-group variabilities and missing data.

The above analysis excluded the Day 14 INR values drawn after liver transplantation. This analysis was done after the medical reviewer corrected the error in INR dataset for the Day 14 INR value of subject (b) (6) (placebo group) from 43 in the submitted INR dataset to 1.43 as shown in the CRF.

The changes in ALT, AST, glucose, sodium, and potassium from baseline to Day 14 were similar between the placebo and the terlipressin groups. The dataset had large amounts of missing values and intra-group variabilities.

Vitals:

Table 27. The Incidence of Hypertension and Hypotension per the Sponsor's Adverse Event Dataset, AEDOSE

MeDRA Preferred Term	**Terlipressin (N= 56) n (%)**	**Placebo (N=55) n (%)**
Hemodynamic		
Hypertension	0	2
Hypotension	4	3

The medical reviewer is not confident about the reported incidence of hypertension with terlipressin in the sponsor's dataset for several reasons. First, the timings of the so-called pre and post dose BPs often conflict with that of study drug administration (b) (6)

Moreover, significant increases in BPs with drug administration are at times not captured as "hypertension" (b) (6)

Table 28. Estimated Mean Change in Blood Pressures (mmHg) with Study Medication

	Terlipressin (N=56) Estimated Mean Change (SE)	**Placebo (N=55) Estimated Mean Change (SE)**
SBP	**3.7 (0.7)**	**-0.4 (0.5)**
DBP	**3.5 (0.5)**	**-0.2 (0.3)**

The vitals dataset excluding the retreatment period was used. A change in blood pressure with drug administration is determined by subtracting the pre-dose from the post-dose blood pressure measurements. The average and standard error of the changes in blood pressure readings with study drug are determined for each subject over the respective study period. Those mean changes in blood pressure per subject are then combined for each treatment group with weights dependent on the above mentioned standard errors.

Data were analyzed after excluding the missing blood pressure readings either the pre- or post-dosing. The analyzed data accounted for 32% of the potential blood pressure measurements pre- and post- drug administration. The effect of terlipressin on blood pressures is difficult to assess considering the high percentage of missing blood pressure data, the lack of conformity between timing of drug administration and pre- vs. post-dose blood pressure readings, and a lack of information on concomitant medications that influence blood pressure (e.g. albumin infusion). Nonetheless, the blood pressure changes shown above seem consistent with that of the sponsor's labeling.

EKGs:

The thorough QT studies were limited by the following issues with methodology:
1) Quantification of the QT effect by the time-averaged method is not acceptable.
2) Almost 50% of patients had no ECGs on Day 7 and 14.
3) 2 paper ECGs were obtained 30 minute apart rather than in triplicates

With these above limitations, the study was adequate to exclude large effects (>30- 60 ms), but not for accurate quantification of the QT effect of terlipressin. An effect on the QT interval is possible and particularly so under conditions of hypokalemia/hypomagnesemia and concomitant medications that prolong the QT interval.

Weights:

The effect of the study medication on weight cannot be evaluated, as only a single measurement of weight prior to starting the study medication was provided by the sponsor.

5.3.2 TAHRS:

Conclusion and Limitations:
This open-label clinical study, intended for publication only, did not support a clinical benefit. Furthermore, this reviewer is not reassured about the safety profile of terlipressin based on this study.

Limitations of TAHRS for Support Approval of Terlipressin for HRS type I Include:

- Open labeled study
- Small size
- High proportion of placebo subjects that received terlipressin rescue
- Unclear which serum creatinine endpoint was prospectively defined
- Inclusion of HRS type II in addition to HRS type I
- Lack of a complete electronic dataset to independent verify the SCr or survival endpoints
- Early termination of the trial due to the observed higher mortality rate in terlipressin arm

Title: Terlipressin in the Treatment of Patients with Hepatic Cirrhosis and Hepatorenal Syndrome (TAHRS). Effects on Survival and Renal Function. Randomized, Prospective, Multicenter Study

Objectives: To investigate the effects of terlipressin and albumin on survival of patients with hepatic cirrhosis and hepatorenal syndrome (HRS) type I and II, and to evaluate whether the improvement in renal function increases the probability of survival.

Period of Study:
First Patient Randomized: January 22, 2002
Last Patient Completed 3-month follow-up: April 28, 2006

Methodology (Design of Study): Open-label, randomized, comparative, albumin-controlled, multicenter

Table 29. The sponsor's Table Enrollment by Investigational Site (ITT Population)

Investigational Site	Hospital Name	Number of Patients Enrolled		
		Terlipressin + Albumin (N=23) n (%)	Albumin (N=23) n (%)	Total (N=46) n (%)
A	Hospital Clinic Barcelona	13 (56.5)	9 (39.1)	22 (47.8)
B	Hospital Sant Pau	1 (4.3)	4 (17.4)	5 (10.9)
D	Hospital del Mar	0 (0.0)	2 (8.7)	2 (4.3)
H	Hospital de Alicante	1 (4.3)	1 (4.3)	2 (4.3)
K	Hospital Puerta del Mar	4 (17.4)	2 (8.7)	6 (13.0)
L	Hospital Insular	2 (8.7)	1 (4.3)	3 (6.5)
P	Hospital Marques de Valdecilla	0 (0.0)	3 (13.0)	3 (6.5)
S	Hospital San Cecilio	1 (4.3)	1 (4.3)	2 (4.3)
V	Hospital Son Llatzer	1 (4.3)	0 (0.0)	1 (2.2)

(Section 5.3.5.1, CSR TAHRS, Table 4.1.2.)
Note, of the above list of participating site, sites B, P, S, and V was not on original list of planned enrollment.

Number of Patients (Planned and Enrolled):
Planned: 100 patients
Enrolled: 46 (46 ITT)
* *The study was terminated after 4 years of enrollment as the result of a protocol-specified interim analysis of survival. The estimated sample size required to demonstrate a significant treatment difference was 431 subjects per treatment group.

Diagnosis and Main Inclusion Criteria (in bold the difference between TAHRS and OT-0401)

Patients 18-75 years old with hepatic cirrhosis and HRS type 1 (a doubling of SCr to ≥2.5 mg/dL in a period of <2 weeks) **or "severe" HRS type 2 (all patients with SCr ≥ 2.0 mg/dL who did not meet the criteria for HRS type 1)**.

Per TAHRS protocol, hepatorenal syndrome was defined according to the criteria of the International Ascites Club (Hepatology 1996; 23: 164-73), same as OT-0401's protocol.

Reviewer Comment: Unlike the design and intent of OT-0401, TAHRS included subjects with HRS type 1 and 2.

B. Exclusion criteria
Exclusion criteria are similar to that in OT-0401. The exclusions criteria that are different from OT-0401 are listed below.

1. Age >75 years
2. Patients with hepatocarcinoma who had more than 3 nodules, a single nodule >5 cm, portal tumor thrombosis, or extrahepatic tumor extension
3. Clinically significant respiratory insufficiency

Test Product, Dose and Mode of Administration:
A. The terlipressin product and the route of administration are the same as in OT-0401. However, the starting dose, the dosing interval and titration parameters are different from that in OT-0401 and are as follows:

- Initial dose of *0.5* mg *every 4 hours*.
- If SCr increased or decreased *<25%* compared with baseline, the dose of terlipressin could be increased to 1 mg every 4 hours on Day 4.
- After another 3 days, the dose could be increased to 2 mg every 4 hours, using the same criteria as for the first dose increase. The maximum dosage permitted was 2 mg every 4 hours.

Furthermore, only the subjects in the control arm receive albumin at the following specified dosage.

B. Control: Human albumin at 20%
Dose: 40 g 20% human albumin (20 g of albumin per vial).
Pharmaceutical form: Liquid vial
Route of administration: Intravenous
Dosage: Administered at an initial dose of 1 g/kg on the first day and 40 g/day on subsequent days, to maintain a central venous pressure between 10 cm and 15 cm water.

Duration of Treatment:
Until one day after the reversal of HRS, or a maximum of 15 days in the event of a negative or partial response

Primary Endpoint:
Survival at 3 months in both treatment groups.

The secondary end-points:
Survival at one month and reversal of hepatorenal syndrome. The parameter used to calculate the sample size is survival at 3 months.

Criteria for patient withdrawal:
1. Ischemia of the extremities manifested by cyanosis, pain and/or decrease in peripheral pulse. (Not specified in OT-0401)
2. Angina and/or myocardial infarction.
3. Symptomatic disturbances in cardiac rhythm or asymptomatic disturbances that meet the following criteria: sinus bradycardia lower than 50 beats/minute or more than 8 ventricular extrasystoles per minute. (Not specified in OT-0401)
4. Signs of intestinal ischemia manifested by persistent abdominal pain and/or gastrointestinal hemorrhage not attributable to other causes.
5. Arterial hypertension with values above 160 systolic and/or 105 diastolic in two consecutive, or three non-consecutive, determinations during treatment.
In patients withdrawn from the study, the clinical and laboratory evaluations specified in the protocol will be completed whenever possible.

Reviewer Comment: TAHRS specified criteria for patient withdrawal based on known terlipressin associated AEs; in contrast, no AE based withdraw criteria was specified in OT-0401, the pivotal study. One may expect some difference in the TEAE profile given this difference in design.

Additional Prohibited Concomitant Treatments (during randomized study) in TAHRS:

1. If indicated, beta-blockers may only be administered during the follow-up period.
2. Plasma expanders, except for albumin.
3. Other non-pharmacological types of treatment that may have an effect on renal function, such as peritoneovenous shunt or intrahepatic portosystemic shunt (TIPS), except in cases of variceal hemorrhage.

4. Spironolactone, given the possibility of causing significant hyperkalemia. During the follow-up period, spironolactone may be administered provided that serum potassium levels are periodically monitored.
5. If intravenous solutions must be administered, only 5% glucose will be administered so

PROTOCOL AMENDMENTS:

1. On April 2, 2003, more than two years after trial commencement, the protocol was amended to allow patients who were randomized to the albumin control group who had experienced treatment failure "the opportunity to receive terlipressin and albumin rescue treatment."
2. On April 2, 2003, the initial dose was changed to 1 mg every 4 hours.

3. PROTOCOL AMENDMENT FROM INTERIM ANALYSIS

After the inclusion of approximately half of the calculated sample size in this open-label trial, the principal investigators conducted a pre-specified interim analysis of the survival data. For this survival analysis, patients who received a transplant or TIPS were censored at the time of the event. A 3-month survival difference of 8% between the 2 groups was observed (27% in the terlipressin + albumin group vs. 19% in the albumin group). Based on these results, the estimated sample size required for demonstrating a significant difference in survival in favor of terlipressin and albumin was 431 patients per group. Considering that this sample size would have been impossible to achieve within a reasonable period of time, the TAHRS study was terminated in June 2006 after 4 years of enrollment at approximately half of the original calculated sample size.

TAHRS DISPOSITION:

Table 30. Adapted from the sponsor's Table - Summary of Patient Disposition

	Terlipressin + Albumin N (%)	Albumin N (%)	Total N (%)
Screened	--	--	67--
Randomized	23 (100.0)	23 (100.0)	46 (100.0)
Treated	23 (100.0)	23 (100.0)	46 (100.0)
Completed 15-day of Treatment	2 (0.09)	4 (0.17)	6 (0.13)
HRS reversal[a]	7 (0.30)	1 (0.04)	8 (0.17)
Withdrawn for noncompliance with protocol	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn for adverse event	5 (21.7)	1 (4.3)	6 (13.0)
Death	5 (21.7)	3 (13.0)	8 (17.4)
Other	4 (17.4)	14 (60.9)	18 (39.1)
Treatment Failure/ Terlipressin Rescue [b]	0 (0.0)	11 (47.8)	11 (23.9)
Complete Response[c]	0 (0.0)	1 (4.3)	1 (2.2)
Error in the Study Inclusion[d]	0 (0.0)	1 (4.3)	1 (2.2)
Family's Decision	1 (4.3)	0 (0.0)	1 (2.2)
Good Response[e]	1 (4.3)	0 (0.0)	1 (2.2)
Poor Clinical Course	1 (4.3)	0 (0.0)	1 (2.2)
Pre-Terminal Condition	1 (4.3)	0 (0.0)	1 (2.2)
Transfer to Another Hospital	0 (0.0)	1 (4.3)	1 (2.2)
ITT	23 (100.0)	23 (100.0)	46 (100.0)
Analyzed for Primary Endpoint	23 (100.0)	23 (100.0)	46 (100.0)
Analyzed for Safety	23 (100.0)	23 (100.0)	46 (100.0)

[a]On Study day 14, none of the subjects in either group had SCr ≤1.5 mg/dL. See section on limitation of TAHRS to support approval of terlipressin based on serum creatinine.
c: Pt (b) (6) experienced HRS reversal. –HRS reversal was defined as complete response, thus this patient should have been included in discontinuation due to HRS reversal portion.
The TAHRS investigators' publication reports only one responder for albumin alone (Patient (b) (6)), as compared with two responders in the OT clinical study report.
d: See 'Protocol Deviations' Section 4.1.3 (Pt (b) (6))
e: Pt (b) (6) experienced HRS reversal, and should have been listed in HRS reversal section
Table summarizes reasons for conclusion of randomized treatment as recorded by investigator on CRF page 33.
(Section 5.3.5.1, CSR TAHRS, Table 4.1.3)

TAHRS Baseline Parameters:

The baseline parameters-demographics, comprehensive metabolic panel, liver function panel, MELD score, vasoactive hormone levels, CBC, and vitals- were all similar with a few exceptions summarized in

Table 31 below.

Table 31. Demographic Data and Baseline Characteristics There were Imbalances Between Treatment Groups.

Parameter	**Terlipressin + Albumin N= 23**	**Albumin N= 23**	**Total N=46**	**P-value [a]**
Body Weight (kg)				
n (%)	17 (73.9)	18 (78.3)	35 (76.1)	
Mean (SD)	76.2 (10.7)	62.8 (12.6)	69.3 (13.4)	0.002[a]
Median	76.3	62.9	68.1	
Min, Max	61.3, 100.0	38.0, 88.0	38.0, 100.0	
Serum Sodium (mmol/L)				
n (%)	23 (100.0)	23 (100.0)	46 (100.0)	
Mean (SD)	124.5 (6.8)	129.1 (7.7)	126.8 (7.5)	0.04
Median	125.0	130.0	126.0	
Min, Max	113.0, 139.0	114.0, 142.0	113.0, 142.0	
Cirrhosis due to AH				
n (%)	14 (60.9)	19 (82.6)	33 (71.7)	0.19

(A Summary of the Sponsor's Tables 4.1.7-12, CSR TAHRS, Section 5.3.5.1)

[a] From ANOVA with main effect treatment for continuous variables. Two-tailed Fisher's exact test was used for test of proportions.

According to the sponsor's tables, baseline body weight and serum sodium showed a statistically significant difference between the two treatment arms. The medical reviewer does not have the baseline demographic dataset to confirm the above results. The body weight (mean and median) was higher in terlipressin group. The mean and median serum sodium were lower in terlipressin group. Hyponatremia is one of the parameters associated with poor survival in HRS; the sponsor suggests subjects in terlipressin group may be sicker than those in placebo group. This reviewer notes that the proportion of subjects with another parameter associated with poor survival, alcoholic hepatitis (AH) status, trended higher in placebo than terlipressin group (p=0.19). In the medical reviewer's opinion, the cumulative impact of the differences in these known, and perhaps other unknown factors, on survival is unclear, particularly for this small sample size where the control for confounders by randomization may not be adequate.

Efficacy Parameters

1. Survival outcomes:

Transplant-free survival and overall survival were analyzed using a two sample log-rank test adjusted for baseline strata (HRS type 1 or 2). In the TAHRS, transplant-free survival was defined as the number of the days from the beginning of the study that each patient survived without receiving a liver transplant. Both transplant and death are counted as events. This approach assumes that a need for liver transplantation indicates a very poor prognosis if not transplanted. In clinical practice, the severity of liver disease and its manifestations are among the criteria for determining the timing liver transplantation; subjects who are sicker (e.g. high MELD scores) generally receive transplant preferentially.

Table 32. Summary of Overall Survival Through Day 90 (ITT Population)

Survived	Terlipressin + Albumin (N=23) n (%)	Albumin (N=23) n (%)	P-value[a]
N	23	23	0.574
Yes	6 (26.1)	6 (26.1)	
No	17 (73.9)	17 (73.9)	
Median Survival (days)[b]	12.0	33.0	

a: From a stratified two-sample log-rank test.
b: Calculated using product limit estimates.

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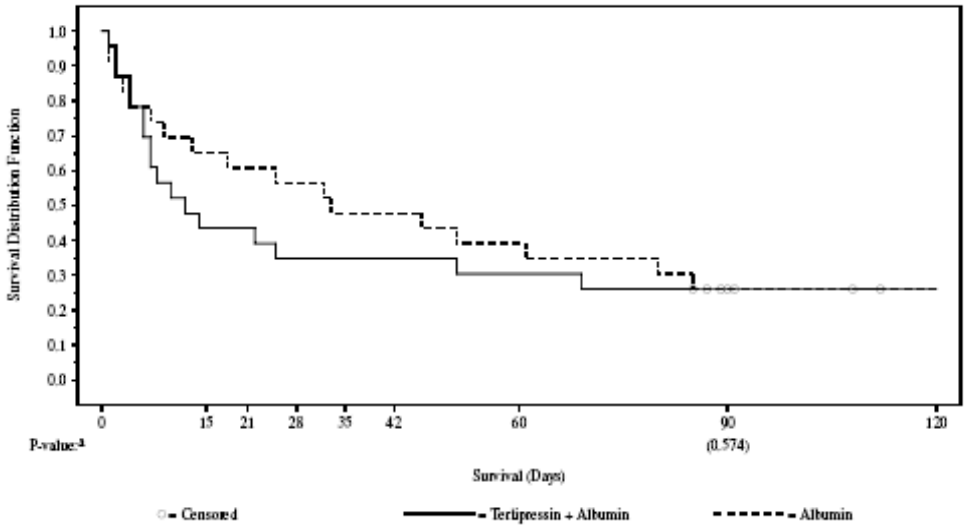
Figure 2. Kaplan-Meier Plot of Overall Survival (ITT Population)



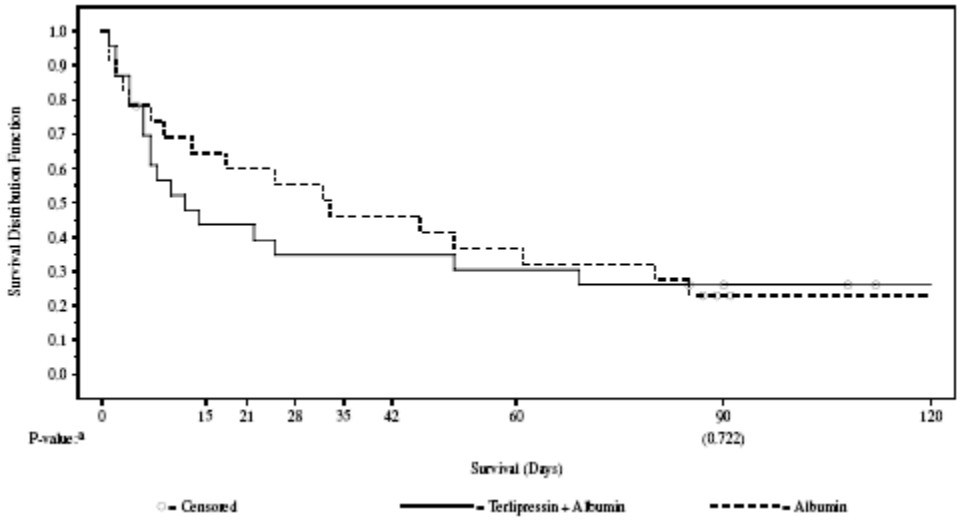
(Source: TAHRS CSR Figure 4.2.6)

Table 33. Summary of Transplant-free Survival Through Day 90 (ITT Population)

Survived	Terlipressin + Albumin (N=23) n (%)	Albumin (N=23) n (%)	P-value[a]
N	23	23	0.722
Yes	6 (26.1)	6 (26.1)	
No	17 (73.9)	17 (73.9)	
Median Survival (days)[b]	12.0	33.0	

a: From a stratified two-sample log-rank test.
b: Calculated using product limit estimates.

Figure 3. Kaplan-Meier Plot of Transplant-free Survival (ITT Population)



(Source: TAHRS CSR Figure 4.2.7)

Based on the above analyses, the sponsor concludes that overall and transplant-free survivals through Day 90 are not significantly different between study groups: 26% overall and transplant-free survival in both treatment groups; p=0.574 (overall survival); p=0.722 (transplant-free survival). On treatment death, however, appears worse in terlipressin group.

Reviewer Comments: In addition to survival through Day 90, attention should also be given to the on-treatment and Day 15 survival data. Terlipressin has a short-half life and activity, and therefore any mortality difference may be diluted by Day 90 in the severely ill, hepatorenal syndrome population. Two, the Day 90 mortality data is likely to be confounded by the significant proportion (48%) of placebo patients that subsequently received terlipressin rescue therapy. Figure 2 and Figure 3 above show higher mortality rates in terlipressin than placebo group. In this reviewer's opinion, this early mortality signal for terlipressin should not be simply dismissed. The reviewers do not have the TAHRS' survival dataset to independent verify the results.

Other endpoints:

HRS Reversal on Randomized Treatment

Note this endpoint does not meet the requirement for sustainable improvement in SCr. Furthermore, currently the sponsor has not provided any information on HRS reversal in HRS type I population.

Table 34. The Sponsor's Tables-Summary of HRS Reversal on Treatment for HRS types 1 and 2 (ITT Population)

	Terlipressin + Albumin (N=23) n (%)	Albumin (N=23) n (%)	P-value[a]
TAHRS	9 (39%) (19.7% - 61.5%)	2 (8.7%) (1.1% – 28.0%)	0.018

[a]From a stratified CMH test

The medical reviewer is not given the dataset to independently verify the result presented in the above table, nor to assess the HRS reversibility in HRS type I patients.

From TAHRS results presented by the sponsor thus far, there is no convincing evidence of clinical meaningful endpoint.

OTHER SAFETY OUTCOMES:

Table 35. Incidence of Treatment Emergent Adverse Events

	Terlipressin + Albumin (N=23)		**Albumin (N=23)**	
	Patients n (%)	**Events n**	**Patients n (%)**	**Events n**
Overall AE	21 (91.3)	78	17 (73.9)	42
Serious AE	17 (73.9)	43	13 (56.5)	22
Nonserious AE	12 (52.2)	35	12 (52.2)	20

Adapted from sponsor's table 4.3.4, CSR section 5.3.5.1. The overall AE were confirmed using sponsor's dataset AEDOSE.

More subjects in the terlipressin group (21 [91%]) experienced AEs compared with placebo group (17 [74%]). Furthermore, more subjects in terlipressin group experienced serious AEs (17 [74%]) compared with placebo (13 [56.5]). The number of AEs experience by subjects in the terlipressin (78) group was higher than control group (42), as well as the number of serious AEs experienced by terlipressin (43) compared with the placebo group (22).

Table 36. Adverse Events Leading to Withdrawal or Interruption of Randomized Study Treatment

Adverse Events Leading to Withdrawal Interruption of Randomized Study Treatment	**Number of Patient N=23 n (%)**
Terlipressin + Albumin group	**5 (22%)**
Intestinal ischemia[a]	3
Volume overload	1
Abdominal distention	1
Pancytopenia[b]	1
Albumin-treated	**2 (9%)**
Circulatory overload	1
Fatal upper GI hemorrhage	1

Abdominal symptoms were the most common causes leading to withdrawal or interruption of the randomized treatment in terlipressin group.

[a]The three cases of intestinal ischemia are as follows:

1) A 56 year old patient developed concurrent abdominal pain and diarrhea after 7 mg of terlipressin. His pain resolved with reduced dose (0.5 mg every 4 hours) of terlipressin, but recurred at full dose.
2) 79 year old man developed abdominal pain, paralytic ileus , elevated CK and LDH levels after 7.5 mg of terlipressin. Abdominal symptoms resolved off terlipressin for two days.
3) 60 year old man developed severe abdominal pain and rectorrhagia on reduced terlipressin dose, after a total of 17 mg of terlipressin.

[b]A 69 year old man developed pancytopenia 3 days post starting terlipressin, after a total of 20mg. He had bone marrow aspiration consistent with medulary aplasia. Off terlipressin, he had resolution of neutropenia on discharge 7 days later.

Table 37. The Sponsor's Table: Adverse Events During the Randomized Treatment Period that Occurred in >10% of Patients within a Treatment Group (Safety Population)

	Terlipressin + Albumin (N=23)		Albumin (N=23)	
MedDRA Term	Patients[a] n (%)	Events n	Patients[a] n (%)	Events n
Diarrhoea	7 (30.4)	8	2 (8.7)	2
Abdominal Pain	5 (21.7)	5	1 (4.3)	1
Hepatic Encephalopathy	4 (17.4)	4	4 (17.4)	4
Acute Pulmonary Oedema	4 (17.4)	4	1 (4.3)	1
Hepatic Failure	3 (13.0)	3	3 (13.0)	3
Hepatorenal syndrome	3 (13.0)	3	3 (13.0)	3
Fluid Overload	3 (13.0)	3	2 (8.7)	2
Dyspnoea	3 (13.0)	3	0 (0.0)	0
Intestinal Ischaemia	3 (13.0)	3	0 (0.0)	0
Anaemia	2 (8.7)	2	3 (13.0)	3
Urinary Tract Infection	1 (4.3)	1	3 (13.0)	3
Vomiting	1 (4.3)	1	3 (13.0)	3
a: Patients are only counted once within a given row.				

(From CSR Section 5.3.5.1, Table 4.3.5)

The above table describes the TEAEs that occurred in >10% of patients. The TEAEs that occurred more frequently in terlipressin than the placebo group are as follows: diarrhea (7 [30%] vs. 2 [9%]), abdominal pain (5 [22%] vs. 1 [4%]), acute pulmonary edema (4 [17%] vs. 1 [4%]), fluid overload (3[13%] vs. 2 [9%]), dyspnea (3 [13%] vs. 0[0%]), intestinal ischemia (3 [13%] vs. 0 [0%]).
The increased respiratory and gastrointestinal symptoms were also seen in OT-0401, although the perceived causes for the respiratory and gastrointestinal symptoms were different between OT-0401 and TAHRS. As an example, while intestinal ischemia was not diagnosed by the investigators in OT-0401, it was diagnosed in 13% of the terlipressin cohort in the open-label TAHRS trial. While acute pulmonary edema and fluid overload were the most common recognized causes of respiratory distress symptoms in TAHRS, bronchospasm/wheezing was the leading cause of respiratory distress symptoms in OT-0401.

6 Appendices

6.1 OT-0401: Narratives of All-Cause Death up to Day 180-Based on Available Study Reports Provided by the Sponsor

Terlipressin

(b) (6) patient with alcoholic hepatitis (AH), recent history of Strep B and Klebsiella bacteremia, was transferred to study site on (b) (6). (b) (6) was started on terlipressin on (b) (6) With 4 days of treatment, SCr remained significantly elevated at 11.8 mg/dL (baseline 11.2 mg/dL), and terlipressin was withdrawn. The cause of withdrawal was coded as "the family opted for a do not resuscitate/do not intubate status". The patient died at 4 hours after terlipressin withdrawal. The cause of death was coded as "multi-organ failure".

(b) (6)
A (b) (6) year old (b) (6) with cirrhosis secondary to hepatitis C "opted to not continue treatment" due to "lack of further treatment options" after 4 days of terlipressin treatment. This decision was made in setting of with worsening renal function, SCr (went from 7.3 mg/dL to 9 mg/dL), and history of vomiting, headache. After discontinuation of terlipressin on (b) (6) patient was switched to octreotide and midodrine for HRS. Subject was at some point started on palliative care (date not provided). (b) (6) died on (b) (6) due to "worsening renal failure."

(b) (6)
A (b) (6) year-old (b) (6) with chronic hepatitis B, inoperable extensive hepatobiliary cancer, a history anemia and thrombocytopenia refractory to multiple transfusions, underwent gemcitabine and oxaliplatin chemotherapy 20 days prior to terlipressin (no work-up provided on whether chemotherapy caused the hematologic side effects). Several hours after starting terlipressin, the patient developed "intense" bilateral thigh pain, "non-serious" right subconjunctival hemorrhage, and "slight" vaginal bleeding. (b) (6) also had "increased confusion". The only hematocrit and platelet provided were 20.7 g/L and $43x10^9$/L, respectively, from 11 days prior to the bleeding.

INR was 1.81 around the time of bleeding. Terlipressin was discontinued after 2 doses. (b) (6) died on (b) (6) due to "worsening renal failure".

(b) (6)
This (b) (6)-year-old (b) (6) subject with hepatitis B, cirrhosis, left leg cellulitis, Aspergillus pneumonia, was treated with 27 doses of terlipressin (b) (6) and unknown amount of albumin (b) (6) with a successful response in SCr. Five days post cessation of terlipressin, subject developed hypoxic respiratory failure, hypotension, ultimately died. Autopsy was significant for pseudomembraneous colitis, and possible gastric variceal bleeding.

(b) (6)
A (b) (6)-year-old (b) (6) patient with AH, recent pneumonia, was treated with terlipressin (33mg total from (b) (6)) and unknown amount of albumin. On these treatments, (b) (6) developed worsening anasarca and pulmonary congestion, failed a trial of furosemide and metolazone, and ultimately required dialysis on day of terlipressin discontinuation (treatment day 6). Despite several dialysis treatments, the patient's severe anasarca did not improve and (b) (6) liver failure progressed. On (b) (6) (the month is likely a typo in CSR the sponsor contacted), patient transitioned to comfort care, and (b) (6) died on (b) (6) due to "liver failure".

(b) (6)
A (b) (6)-year-old (b) (6) patient with AH, was hospitalized for increasing confusion and weakness. (b) (6) was treated with terlipressin (5 mg total, on (b) (6)) and albumin 25mg IV q6 hour from (b) (6). Despite some improvement in SCr, (b) (6) mental status and "overall clinical status" continued to deteriorate. Terlipressin was discontinued on Day 2 as (b) (6) transitioned to comfort care. (b) (6) died at home hospice on (b) (6) due to "end-stage liver disease".

(b) (6)
A (b) (6)-year-old (b) (6) patient with AH was hospitalized with hematemesis from severe portal hypertensive gastropathy. The patient was not a transplant candidate due to recent alcohol use. The patient was treated with 7 mg of terlipressin from (b) (6). On terlipressin, the patient's condition continued to deteriorate; (b) (6) developed hepatic encephalopathy, recurrent ascites and multi-organ failure. (b) (6) was transitioned to comfort care, and terlipressin was discontinued. The patient died on 18 hours later on (b) (6) due to "multi-organ failure".

(b) (6)
A (b) (6)-year-old (b) (6) patient with hepatitis B, cirrhosis was treated with 7 doses of terlipressin from (b) (6) On terlipressin, he had 3 episodes of hemoptysis on (b) (6). Pulmonary hemorrhage was suspected. INR was 3.7 on (b) (6), 2.4 on (b) (6); Hemoglobin was 10.7 and platelet 78 X 10^3 on (b) (6) The patient was intubated due to hypoxia and ARDS. (b) (6) SCr doubled from treatment day 0 to day 2. On treatment day 2, terlipressin was discontinued because "family decided to discontinue treatment", and the patient died on the same day. The time of death was not provided. No autopsy was performed.

(b) (6)
A (b) (6)-year-old (b) (6) patient with AH was hospitalized on (b) (6) acute liver failure secondary to with an unintentional acetaminophen overdose (unclear if (b) (6) also had baseline liver disease), and was found with anuric acute renal failure. (b) (6) received terlipressin (18 mg from (b) (6) and unknown amount of albumin on (b) (6) On (b) (6) the patient was found to have a new bilateral pneumonia and volume overload with pulmonary edema, for which (b) (6) was treated with high dose furosemide (b) (6) and chlorothiazide (b) (6). (b) (6) died due to "sepsis" at (b) (6) 1 hour and half after the last dose (according to the original recorded time on CRF). No autopsy was performed.

(b) (6)
A (b) (6)-year-old (b) (6) patient with AH, encephalopathy, recent history of pneumonia requiring ventilatory support, and Candida albicans sepsis (discovered after enrollment), was treated with 6 mg of terlipressin (b) (6) and unknown amount of albumin. (b) (6) was taken off terlipressin due to a need for dialysis for "possible ARDS" that ultimately required ventilatory support. After initial response to continuous hemodialysis, (b) (6) respiratory status remained tenuous and she required multiple episodes of intubation for "pneumonia" and dialysis for "fluid overload" during (b) (6) hospitalization. On (b) (6), (b) (6) refused reintubation. On (b) (6), (b) (6) was transitioned to comfort care. (b) (6) died on (b) (6) due to "sepsis and bilateral pneumonia".

(b) (6)
A (b) (6)-year-old (b) (6) patient with AH, hydrothorax, ascites, was treated with after 70 mg of terlipressin (b) (6) and intermittent albumin with improved SCr. During terlipressin treatment, (b) (6) developed worsening hydrothorax and ascites requiring therapeutic thoracentesis, paracentesis (treatment day 3), and spironolactone (treatment day 8, 10 and onward). After discontinuing terlipressin on treatment day 11 due treatment success, the patient refused the therapeutic paracentesis and was discharged home on the same day. (b) (6) respiratory status was apparently fair on discharge. On (b) (6), patient developed shortness of breath, refused medication or further medical evaluation. (b) (6) died approximately 3 hours later. No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient with cirrhosis secondary to hepatitis C and hepatocellular carcinoma, was treated with 55 mg terlipressin from (b) (6) and undisclosed amount of albumin (b) (6) The patient was alive on the 90-day follow-up. On (b) (6) the site was informed by a family member that the patient had died. The patient's local physician confirmed that the patient had died approximately 3 weeks earlier. The cause of death was not specified and the exact date of death is still not provided by the sponsor.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, was treated with 9 mg of Terlipressin (b) (6) without concomitant albumin administration. On (b) (6) (treatment day 3), (b) (6) developed respiratory distress, evidence of "alveolar hemorrhage", pulmonary edema and

metabolic acidosis, refractory to IV furosemide. Terlipressin was discontinued due to "physician decision". (b) (6) ultimately required ventilatory support and continuous veno-venous hemodialysis on (b) (6) (b) (6) intubation was complicated by transient asystole. On (b) (6), the patient developed septic shock. On (b) (6) the patient was found in asystole. No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH and lower leg cellulitis (treated and apparently controlled with cefepime), was started on terlipressin on (b) (6) On (b) (6) after a total of four doses of study medication, the patient developed burning pain in both lower extremities and signs of livedo reticularis. With discontinuation of terlipressin, livedo reticularis resolved on subsequent day. Burning leg pain was not recorded in AE dataset, and its duration was not reported. (b) (6) required continuous veno-venous hemofiltration on (b) (6) for worsening renal failure, severe academia, and hypotension. (b) (6) had evidence of sepsis on (b) (6). (b) (6) died on (b) (6) due to "multi-system organ failure".

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, was hospitalized on (b) (6) with hepatic encephalopathy and severe ascites. (b) (6) was treated with 100 mg of terlipressin from (b) (6) and albumin (total amount unknown) from (b) (6) On these therapies, (b) (6) developed radiographic evidence of increasing pulmonary edema (b) (6) Work up for pulmonary edema with transesophageal echocardiogram on (b) (6) revealed a dilated, hypertrophied left ventricle with infero-posterior akinesis and an ejection fraction of 30-35% (unclear old or new). (b) (6) was treated with 13 doses of intravenous furosemide intermittent during terlipressin therapy. (b) (6) was also required intubation on (b) (6). The pulmonary edema resolved on (b) (6). (b) (6) weight change and fluid balance with respective therapy described above were not provided. (b) (6) was transferred to hospice care on (b) (6). (b) (6) died on (b) (6) due to "end-stage liver disease".

(b) (6)
"Respiratory distress; Myocardial infarction; Multi-organ system failure; Enterococcal sepsis"
This (b) (6)-year-old (b) (6) patient status post a transjugular intrahepatic porto-systemic shunt (TIPS) was placement for refractory ascites on (b) (6), was started on terlipressin on (b) (6) On (b) (6), approximately one hours after terlipressin (at 2mg level) the patient developed hypoxic respiratory distress (required intubation), and relative hypotension BP 85/59 (pre-dose BP 113/76 and HR 102), and mottling of both lower extremities (unclear if liveodo reticularis). ECG and cardiac enzyme and subsequent ECHO (b) (6) were consistent with myocardial infarction; and angiograph did document significant CAD. (b) (6) was not ruled out for pulmonary emboli. Furthermore, (b) (6) also developed enterococcal sepsis. Terlipressin was discontinued on (b) (6) (after a total of 20 mg). The myocardial infarction and enterococcal sepsis resolved on (b) (6)

The patient remained largely dependent on ventilatory support. (b) (6) developed recurrent pleural effusions, and biopsy proven pulmonary hemorrhages (dates unable to be provided by the

sponsor). Three days before (b) (6) death, the patient developed a Candida UTI accompanied by recurrent enterococcal bacteremia. (b) (6) died on (b) (6) due to multi-organ system failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient was started on terlipressin on (b) (6) for acute increase in creatinine in the setting infection. Terlipressin was discontinued on (b) (6) (after 31 mg) as the patient's SCr had decreased to 0.9 mg/dL and patient was discharged.
Since stopping treatment, his SCr went up to 1.5 mg/dL on (b) (6) and
2.3 mg/dL on (b) (6). (b) (6) was re-hospitalized on (b) (6) with septic shock secondary to spontaneous bacterial peritonitis and portosystemic encephalopathy. The patient died on (b) (6) (b) (6) due to sepsis and spontaneous bacterial peritonitis. The family declined an autopsy.

(b) (6)
This (b) (6)-year-old (b) (6) patient with hepatitis C, AH, without a prior history of refractory ascites, cardiac disease, or "respiratory system past medical history", but had "shortness of breath" at baseline per CRF at on (b) (6) Terlipressin was started on (b) (6) and continued despite a diagnosis of acute tubular necrosis on (b) (6) On (b) (6) apparently half an-hour before the 4th dose of terlipressin per dosing dataset, patient developed hypoxia and fluid overload, required IV furosemide without diuresis. Cardiac and DVT workups were negative.

On (b) (6) (b) (6) heart rate was increased from baseline of 80s to 90s bpm to 109 and 117 bpm on pre- and post- 8th dose of terlipressin, respectively. Four hours after the 8th dose of terlipressin, during dialysis for fluid removal, (b) (6) developed rapid atrial fibrillation (175bpm) along with chest pain, EKG evidence of ischemia. The patient received the 9th dose of terlipressin, within 2 hours after dialysis. The pre- and post- 9th dose vitals were "not recorded". Apparently, the patient did not improve after dialysis and was then started on comfort care. The patient died on the evening of (b) (6) due to "pulmonary edema". No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient was hospitalized on (b) (6) with hypotension and hypothermia, several days after a large volume paracentesis. The patient was started on terlipressin on (b) (6). The patient completed the maximum protocol specified treatment period on (b) (6) after 79 mg of terlipressin. The patient was not considered a transplant candidate due to hepatocellular carcinoma with metastasis to the portal vein. (b) (6) was discharged to home hospice care on (b) (6), and died on (b) (6) due to liver failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient was randomized and started on terlipressin on (b) (6)
Terlipressin was discontinued on (b) (6) (35mg) due to a decrease in SCr. Subsequently, the patient had a rapid rise in bilirubin levels and was found with late stage liver cancer. The patient was discharged to home hospice and died 4 days later on (b) (6)

(b) (6)

This (b) (6)-year-old (b) (6) patient, without a prior history of esophageal variceal hemorrhage, was treated with 40 mg of terlipressin from (b) (6) After discontinuing protocol terlipressin due to treatment failure, (b) (6) was initiated on open-label terlipressin (marketed commercial product) and midodrine from (b) (6). The total doses of these two open label therapies were not provided.
On (b) (6), the patient developed "life-threatening acute esophageal variceal bleeding", which responded to ligation. On (b) (6) the patient again developed life-threatening acute variceal bleeding which resolved with Histoacryl injection. On (b) (6), the patient apparently developed pulmonary embolism from Histoacryl particles, complicated by post-infarct pneumonia, respiratory insufficiency, and SIRS. The patient died on (b) (6) No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient was treated with a total of 9 mg of terlipressin from (b) (6) to (b) (6). On (b) (6) terlipressin was discontinued due to "the need for hemofiltration dialysis". Also on (b) (6) the patient was transferred to the ICU for stabilization of hemodynamic parameters with catecholamine administration. Patient's vitals post the last dose of terlipressin and the onset of the hemodynamic instability that resulted in ICU transfer were not provided. The patient's ICU stay was complicated by development of Staphylococcus aureus sepsis on (b) (6). The patient died on (b) (6) due to multiple organ failure and sepsis.

(b) (6)
This (b) (6)-year-old (b) (6) with AH was treated with a total of 56 mg of terlipressin over 14 days, (b) (6). On (b) (6), the patient had a transitory increase in SCr to 2.4 mg/dL and hepatic insufficiency worsened. The patient died on (b) (6) due to hepatic insufficiency. An autopsy performed on (b) (6) confirmed "the direct cause of death as hepatic insufficiency".

(b) (6)
This (b) (6)-year-old (b) (6) patient without any indication of baseline encephalopathy documented on CRF, was treated with a total of 56 mg of terlipressin over 14 days, from (b) (6) "Subsequently" (date not provided), "the patient's encephalopathy progressed to coma". (b) (6) died on (b) (6) An autopsy confirmed that "the direct cause of death was reported to be increasing hepatocellular insufficiency".

(b) (6)
This (b) (6)-year-old (b) (6) patient was treated with 56 mg of terlipressin over 14 days, from (b) (6). The patient was discharged on (b) (6) The patient was rehospitalized on (b) (6) with abdominal pain, dyspnea, and fever. Pleuritis and an acute abdomen were diagnosed. Despite therapies, the patient's condition worsened. The patient died on (b) (6) due to "hepatic insufficiency".

(b) (6)

This is a (b) (6)-year-old (b) (6) patient with AH, encephalopathy, anuria, was treated with 2 mg of terlipressin on (b) (6) In less than two hours after terlipressin, the patient died "after a cardiac arrest due to hepatic insufficiency." No autopsy was performed

(b) (6)
This (b) (6)-year-old (b) (6) patient with alcoholic hepatitis, no indication of a baseline encephalopathy per CRF, was hospitalized on (b) (6) with jaundice, ascites and leg edema. The patient was started on terlipressin on (b) (6) Approximately one hour after the third dose of terlipressin on (b) (6) (1:20h per CRF), (b) (6) became hypotension (80/40) and tachycardia (116), and her "encephalopathy progressed into a coma". (b) (6) died an hour later. No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient with alcoholic cirrhosis was started on terlipressin on (b) (6) Approximately 3 hours after the second dose of terlipressin, the patient had an asystolic cardiac arrest and died. An autopsy reportedly "confirmed the cause of death was hepatic insufficiency due to alcoholic cirrhosis".

(b) (6)
This (b) (6)-year-old (b) (6) patient was hospitalized on (b) (6) with cirrhosis, portal hypertension, ascites, jaundice and a 1-week history of deteriorating medical condition, was started on terlipressin on (b) (6) Within 2 hours after the third dose of terlipressin, (b) (6) "encephalopathy progressed to coma" (though no known baseline encephalopathy per CRF record) and heart rate and blood pressure became undetectable. Resuscitation efforts were unsuccessful and the patient died on (b) (6) No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient was hospitalized on (b) (6) with alcoholic cirrhosis, ascites, jaundice, lower extremity edema, was started on terlipressin was started on (b) (6) Two hours after the second dose of terlipressin, BP starts to trend lower (from 110/70 mmHg pre-dose to 90/60 mmHg post-dose). The patient's general condition continued to decline and " (b) (6) encephalopathy" worsened (although (b) (6) had no indication of baseline encephalopathy on CRF on the date of randomization, (b) (6). The patient became hemodynamically unstable and (b) (6) died within 6 hours post last dose of terlipressin. No autopsy was performed.

Placebo:

(b) (6)
This (b) (6)-year-old (b) (6) patient was treated and discharged after a 14-day therapy with placebo (b) (6) along with furosemide (b) (6) and with unknown amount of albumin. After the discharge, (b) (6) was twice re-hospitalized for acute renal insufficiency, attributed "overdiuresis". On the (b) (6) hospitalization, (b) (6) was also found bacterial peritonitis, which resolved on an unspecified date. (b) (6) was later found with worsening primary hepatocellular carcinoma and transferred to home hospice care on (b) (6) (b) (6) died on (b) (6)

This (b) (6)-year-old (b) (6) patient with cirrhosis, concern for upper GI bleed (endoscopy negative for active bleed), was started was treated with placebo from (b) (6) A vasopressin infusion was subsequently administered from (b) (6) (b) (6) was transferred to comfort/palliative care and died on (b) (6) "due to hepatorenal syndrome".

This (b) (6)-year-old (b) (6) patient was admitted on (b) (6) with encephalopathy, Clostridium difficile colitis, known coagulase negative staphylococcus bacteremia on continued antibiotic treatment, was started on placebo on (b) (6) Several hours after first dose of placebo, the investigator discontinued the study medication due to a notification of the subject's endocarditis on the pre-study cardiac echocardiogram. On (b) (6) dialysis was initiated. During dialysis on (b) (6), the patient developed supraventricular tachycardia without hypotension or neurologic changes. On (b) (6) the patient developed atrial fibrillation, rate controlled with diltiazem. On (b) (6) and the patient was transferred to Palliative Care, and (b) (6) died due to hepatorenal syndrome on (b) (6)

This (b) (6)-year-old (b) (6) patient was started on placebo on (b) (6) The patient completed the protocol-specified 14-day treatment period on (b) (6) The patient was discharged from the hospital on an unspecified date and did not return for any follow-ups. The investigator contacted the patient's local gastroenterologist and was informed that the patient died on (b) (6) due to multi-organ failure.

This (b) (6)-year-old (b) (6) patient was initially treated with midodrine ((b) (6) and octreotide (b) (6) for rising SCr. The patient was then treated with placebo from (b) (6) Midodrine and octreotide were restarted after stopping placebo. The patient was discharged to home hospice care on (b) (6). (b) (6) died at home on (b) (6) "due to multi-organ failure".

This (b) (6)-year-old (b) (6) patient was treated with 7 doses of placebo from (b) (6) before transition to comfort care. The patient died on (b) (6) due to "hepatorenal syndrome".

This (b) (6)-year-old (b) (6) patient was treated with placebo from (b) (6). Placebo was stopped when he required hemodialysis.
On (b) (6) the patient developed acute and brisk proximal gastric variceal bleed, treated with vasopressin, embolization, and TIPS. (b) (6) prolonged hospital course was complicated by pneumonia, ARDS requiring intubation and eventual tracheotomy, bacteremia, and hemodialysis. (b) (6) was transitioned to palliative/comfort care on (b) (6) and (b) (6) died on (b) (6) "due to end-stage liver disease".

(b) (6)

This (b) (6)-year-old (b) (6) patient was started on placebo on (b) (6). (b) (6) liver failure and encephalopathy worsened. (b) (6) developed coagulopathy and required FFP and Factor VII treatment. The patient had acidosis and had a positive fluid balance due to renal failure. Comfort care was started on (b) (6) and placebo was discontinued. The patient died on (b) (6) due to liver failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient with cirrhosis (unclear etiology), variceal bleed, and ascites, was started on placebo on (b) (6). Placebo was discontinued on (b) (6) due to decrease in creatinine to 1.1.
(b) (6) subsequent course was complicated by pneumonia, encephalopathy. (b) (6) was transferred to home hospice care where she died on (b) (6)

(b) (6)
This (b) (6)-year-old (b) (6) patient with acute liver failure, attributed to chronic hepatitis B +/- drug-induced liver disease, was started on placebo on (b) (6). On (b) (6) the patient was more lethargic and confused with progressive renal deterioration. Neurologic differential diagnosis was Parkinson's disease versus supranuclear palsy. On (b) (6), placebo was discontinued because of dialysis need. On (b) (6) all life-sustaining care, including dialysis was withdrawn and supportive care continued. The patient died on (b) (6) due to liver failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient with acute valproate-induced liver failure was treated with placebo from (b) (6) to (b) (6) with treatment success by SCr measure. Subsequently, after two re-hospitalizations for encephalopathy, (b) (6) was transferred to a long-term facility for convalescence on (b) (6) On (b) (6), (b) (6) became apneic after aspiration of gastric contents and died despite resuscitation efforts.

(b) (6)
This (b) (6)-year-old (b) (6) patient was started on placebo on (b) (6). Study medication was discontinued after only 2 doses due to initiation of dialysis. The patient received a liver transplant on (b) (6) Postoperatively, while his renal function and urine output initially improved, he subsequently developed anuria acute renal failure in setting of Klebsiella peritonitis, Fusobacterium bacteremia, septic shock, and ultimately required CVVHD (b) (6). On (b) (6), (b) (6) code status was changed to DNR. He was extubated and placed on a morphine infusion. The patient died on (b) (6) due to peritonitis, anuria and acute respiratory distress.

(b) (6)
This (b) (6)-year-old (b) (6) patient was started on placebo on (b) (6) Study medication was discontinued on (b) (6) due to the initiation of dialysis. On (b) (6) during dialysis treatment on, the patient became hypotensive (65/30 mm Hg) and unresponsive, and was found to be in rapid atrial fibrillation. Dialysis was discontinued, and (b) (6) was transitioned to palliative care. (b) (6) was discharged to a hospice facility on (b) (6) and died on (b) (6) due to renal failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, pulmonary infection, pulmonary edema, and worsening hypoxic respiratory distress, was treated with 4 doses of placebo from (b) (6) (b) (6) was intubated for hypoxic respiratory failure after one dose of placebo. Despite receiving doses of IV furosemide, he was continued on placebo until (b) (6) (b) (6). On (b) (6), (b) (6) was transitioned to comfort measure, placed on a terminal-wean protocol and died from respiratory failure half-hour later. No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, recent alcohol withdrawal syndrome, was treated with 11 doses of placebo (b) (6) (b) (6) renal and liver functions continued to decline, and placebo was discontinued. The patient was discharged on (b) (6) and died at home on (b) (6) due to end-stage liver disease.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, recent abstinence, CAD, PAD, renal failure despite midodrine and octreotide, was started on placebo on (b) (6) Placebo was discontinued on (b) (6) after 29 doses (45 mg total) when patient elected to leave the hospital against medical advice. At the 60-day follow-up, on (b) (6), the patient was hospitalized (for unspecified reason) and had not received dialysis or liver transplant. (b) (6) reportedly had died on (b) (6) due to liver disease.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, was treated with 28 doses (44 mg) of placebo from (b) (6) (b) (6) was discharged from the hospital on (b) (6) without dialysis.

Subsequently, (b) (6) was re-hospitalized three times. From (b) (6), (b) (6) was with admitted with worsening hepatic encephalopathy and was started on hemodialysis (b) (6). From (b) (6), (b) (6) was admitted for gram-negative bacteremia and malnutrition. (b) (6) stay was complicated by ischemic colitis (in setting of midodrine use for hypotension on dialysis), hypoxia, UTI, vaginal bleeding, skin ulcers. On (b) (6), (b) (6) was re-admitted with fever and hypotension, and found with melanotic stools and positive culture (type unknown) for vancomycin-resistant enterococcus. (b) (6) was transitioned to Palliative Care, and died on (b) (6) due to end-stage liver disease.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, and no known respiratory history, was treated with 19 doses (25 mg) of placebo (b) (6) and unknown doses of albumin (b) (6) . On (b) (6) (b) (6) developed respiratory distress with pulmonary edema, hypoxia, respiratory acidosis, and required ventilatory support. Placebo was permanently discontinued. (b) (6) hematocrit also decreased (no lab values provided). (b) (6) was transitioned to comfort care and died on (b) (6)

(b) (6)
This (b) (6)-year-old (b) (6) patient with cryptogenic cirrhosis, exacerbation of portal systemic encephalopathy, left lower lobe pneumonia, and C difficile colitis, chronic renal insufficiency with further acute decline attributed to "myoglobinuria" "precipitated" HRS. The patient was started on placebo on (b) (6) On (b) (6) a urinary tract infection due to enterococcus and Candida was diagnosed. Placebo was discontinued on (b) (6) (after 27 doses, a total of 42mg). On (b) (6), (b) (6) was transitioned to comfort measures only and a morphine drip was started. The patient died on (b) (6) due to "renal failure".

(b) (6)
This (b) (6)-year-old (b) (6) patient with cirrhosis due to AH was started on placebo on (b) (6) Placebo was discontinued on (b) (6) after 18 doses/24mg total, as the "patient withdrew consent for administration of placebo." Hemodialysis was initiated on (b) (6). (b) (6) died on (b) (6) due to terminal liver failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient with a recent and significantly decline in cardiac output (EF 35% on (b) (6)) was started on placebo on (b) (6). (b) (6) had a repeat cardiac echocardiogram on (b) (6) which revealed global hypokinesis and a further decline in EF to less than 20%. (b) (6) was removed from the liver transplant list and discharged to home hospice care on (b) (6). (b) (6) died on (b) (6) due to "diabetic cardiomyopathy."

(b) (6):
This (b) (6)-year-old (b) (6) patient with adrenal insufficiency, persistent and severe Klebsiella pneumoniae peritonitis (peritoneal fluid on (b) (6) WBC 14,200/uL, 93% poly cells), was started on placebo on (b) (6). On (b) (6) the patient became hypotensive and developed leukocytosis. One hour after the 12th and last dose of placebo, (b) (6) developed increasing somnolence and "difficulty swallowing", but vital signs did not changed. Two hours post last dose, "the nurse found the patient to be apneic and the patient was pronounced dead." No autopsy was performed.

(b) (6)
This (b) (6)-year-old (b) (6) patient was started on placebo on (b) (6) On 1 (b) (6), (relationship to dose unknown) (b) (6) developed subcostal discomfort, difficulty sleeping, and an intermittent but self-limited arrhythmia. An ECG revealed premature atrial complexes and persistent, possibly worsened inverted T waves anteriorly. Cardiac enzymes were negative for myocardial infarction and (b) (6) remained hemodynamically stable. The dose of placebo was increased on (b) (6) per protocol. On placebo, (b) (6) encephalopathy and renal impairment worsened. On (b) (6), all medical treatments, including placebo, were discontinued as (b) (6) was transferred to comfort care. (b) (6) died the same date due to hepatorenal syndrome.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, hepatitis C, was hospitalized for refractory ascites, fever, and abdominal pain. During (b) (6) prolonged hospitalization, (b) (6) developed encephalopathy, acute respiratory distress syndrome and transfusion related acute lung injury that had required

intubation, and renal impairment. (b) (6) was started on placebo on (b) (6). After two doses of placebo, (b) (6) refused all further treatment, including a liver transplant, and left the hospital against medical advice on (b) (6) The patient died at home on (b) (6) due to "hepatorenal syndrome".

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, ascites, developed acute renal failure after large volume paracentesis (b) (6) and furosemide. For his renal impairment, (b) (6) was initially treated with midodrine, octreotide, but was then started on placebo on (b) (6). Placebo was discontinued on (b) (6) when patient left the hospital against medical advice, "stating (b) (6) was feeling better and did not wish further treatment." The patient died on (b) (6) due to "liver failure" while in home hospice care.

(b) (6)
This (b) (6)-year-old (b) (6) patient with cirrhosis secondary to hepatitis C, grade 3 ascites, was started on placebo on (b) (6). Placebo was discontinued on (b) (6) as the patient withdrew consent, declined further treatment, and requested discharge from the hospital. The patient was discharged on (b) (6) The patient returned to (b) (6) home country and died at home on (b) (6) due to terminal liver failure.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, hepatitis C, hepatic encephalopathy was started on placebo on (b) (6) On treatment day 2, blood culture drawn on (b) (6) resulted gram positive diptheroides (no additional information on blood culture was provided). (b) (6) was treated with broad spectrum antibiotics, but developed progressive hemodynamic instability. On (b) (6), dopamine was initiated, followed by midodrine and octreotide (b) (6) Placebo, supposedly discontinued after the initiation of the other pressor agents, was administered intermittently until (b) (6) (for a total of 27 doses/27 mg). In addition, (b) (6) developed worsening hepatic encephalopathy, progressive azotemia, acidosis and fluid overload. On (b) (6), the patient died due to "terminal liver failure". In the survival dataset, the death date was listed as (b) (6).

(b) (6)
This (b) (6)-year-old (b) (6) was treated with placebo from (b) (6) Following discontinuation of placebo for treatment failure, dialysis was administered from (b) (6) Open-label terlipressin (marketed product) was then administered from (b) (6) (b) (6) was discharged on an unspecified date, and reportedly died on (b) (6)

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, was started on placebo on (b) (6) At midnight on (b) (6), placebo was discontinued after 8 doses, due to need for dialysis. On (b) (6) more than 4 months after the cessation of placebo, the patient developed acute gastric ulcer bleeding and decompensation of liver cirrhosis and died the same day. Dialysis treatments were ongoing at the time of death. Gastric ulcer was listed as an AE in the sponsor's AEDOSE dataset.

(b) (6)
This (b) (6)-year-old (b) (6) patient with a hemochromatosis, history of esophageal variceal hemorrhage, bleeding hypertensive gastropathy, anemia; thrombocytopenia, was started on placebo on (b) (6). On (b) (6), (b) (6) developed intra-abdominal bleeding due to massive venous collaterals. On (b) (6) placebo was discontinued after 9 doses and dialysis was initiated.
Open-label terlipressin (marketed product) was subsequently administered from (b) (6) until (b) (6) at a dose of 1 mg four times per day. On (b) (6) the patient underwent an exploratory laparotomy and 8 liters of blood were removed from the abdominal cavity. No information was provided on what led to the procedure. Postoperatively, the patient developed "signs of disseminated intravascular coagulation and hypovolemic shock", "acute cardiac insufficiency due to intracardiac thrombosis and blood loss". The patient died on (b) (6)
No autopsy was performed.
Intra-abdominal bleeding, acute cardiac insufficiency, intracardiac thrombosis were attributed to placebo therapy in the sponsor's dataset.

(b) (6)
Intraperitoneal Hemorrhage, Worsening Atrial Fibrillation
This (b) (6)-year-old (b) (6) patient with AH, intermittent atrial fibrillation, was treated with placebo from (b) (6) During placebo treatment period, she reportedly developed "worsening" atrial fibrillation, details of worsening not provided.
From (b) (6), the patient was treated with open-label terlipressin (marketed product) at a dose of 3 mg/day. On (b) (6), (b) (6) underwent a transjugular intrahepatic portosystemic shunt (TIPS) for refractory ascites, which was complicated by an extrahepatic portal vein dissection. The patient died (b) (6) due to intraperitoneal hemorrhage.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, anemia, but no known esophageal varices, was started on placebo on (b) (6) On (b) (6), the patient developed melena, blood pressure decreased to 70/20 mm Hg and (b) (6) mental status progressed to "precoma". Endoscopy revealed bleeding from esophageal varicose veins. In spite of resuscitative efforts, the patient died at (b) (6) due to esophageal variceal hemorrhage. Per autopsy, the direct cause of death was post-hemorrhagic anemia due to esophageal bleeding from esophageal varicose veins.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, a recent history of "increasing breathlessness" (b) (6), marginal baseline BP (pre-randomization, BP 80-90/60, HR 78-110), but no history of arrhythmia, was started on placebo and an increase dose of albumin on (b) (6) One and half hours after the second dose of placebo (time to albumin not provided), the patient developed increasingly dyspneic and signs of pulmonary edema. A half hour later, (b) (6) developed respiratory arrest and was found with ventricular fibrillation. (b) (6) was intubated and sinus rhythm and consciousness were restored within five minutes. Vasopressors were started on (b) (6) for hypotension (BP 80/50 mm Hg), and placebo was discontinued after 5 doses. The patient died on (b) (6). The autopsy revealed shallow (small) nodular monolobular cirrhosis,

esophageal and cardia varicose vein dilation, ascites, splenomegaly, parenchymatous jaundice, pulmonary edema, cerebral edema.

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, was started on placebo on (b) (6) Placebo was discontinued on (b) (6) due to treatment success. The hepatic insufficiency worsened beginning on (b) (6). The patient died on (b) (6) due to "hepatic insufficiency."

(b) (6)
This (b) (6)-year-old (b) (6) patient with AH, portal hypertension, jaundice, ascites, and recent esophageal variceal bleed (b) (6) was started on placebo on (b) (6). On (b) (6) more than 3 hours after the third dose of placebo, (b) (6) "heart rate and blood pressure became undetectable and (his) encephalopathy progressed to coma". The patient died at (b) (6) . Autopsy report demonstrated "shallow (small) nodular cirrhosis complicated by acute post hemorrhagic anemia."

Safety Narratives on "Serious Adverse Events" Up to 30 Days Post Treatment
The Summary is Based on Available Information Provided by the Sponsor

TERLIPRESSIN
(b) (6)
Supraventricular tachycardia 16-beat run; Dyspnea worsened; Fall ground level
This (b) (6)-year-old (b) (6) patient with AH, a negative respiratory or cardiac history, was initiated on terlipressin on (b) (6)
On (b) (6), a chest x-ray revealed interstitial edema and bilateral pleural effusions.
On (b) (6). (b) (6) was noted to be oriented to self, place and events and denied head injury.
On (b) (6), (b) (6) developed a 16-beat run of supraventricular tachycardia, but was asymptomatic and did not require any medical intervention.
Thirty minutes after a transfusion of one unit PRBC on (b) (6) for a hemoglobin of 6.8 (no prior hemoglobin provided), the patient developed shortness of breath, hypoxia (pulse oximetry decreased to 69%) and hypotension (blood pressure decreased to 82/56 mm Hg). (b) (6) was placed on a non-rebreather oxygen mask and treated with 40 mg of furosemide. Temperature and heart rate remained normal before, during and after the transfusion.
By (b) (6), the patient had been weaned off the 100% non-rebreather and pulse oximetry had increased to 90% on 4L oxygen via nasal canola.
Terlipressin was discontinued on (b) (6) after 27 doses due to a sustained decrease in SCr.
At the final 180-day follow-up, the patient was alive and had not required dialysis or received a liver transplant.

(b) (6)
Peritonitis
This (b) (6)-year-old (b) (6) patient with AH and refractory ascites, was treated with terlipressin from (b) (6). On (b) (6), (b) (6) developed peritonitis, for which (b) (6) was treated with fluconazole, vancomycin, ceftriaxone, and piperacillin/tazobactam. The peritonitis resolved on

(b) (6). On (b) (6) (b) (6) was discharged home and on maintenance dialysis 3 times per week. On (b) (6), he received a liver transplant and continued to receive dialysis post transplantation until (b) (6). At the final 180-day follow-up, the patient was alive and was not receiving dialysis.

(b) (6)
Asystole
This (b) (6)-year-old (b) (6) patient was treated with 26 doses of terlipressin from (b) (6) (b) (6) Terlipressin was discontinued 3 hours before his liver transplantation. Intraoperatively, more than 6 hours after (b) (6) last terlipressin dose, (b) (6) developed a brief period of asystole (<30 sec) after unclamping of his IVC and portal vein. Atropine and epinephrine were administered and the surgeon provided internal compressions until return of spontaneous heart rate.
The postoperative course was complicated by ileus which resolved spontaneously on postoperative Day 8. The patient was discharged on (b) (6) At the 180-day follow-up, the patient was alive and had not received dialysis.

(b) (6)
Renal failure; Ventricular tachycardia; Pneumonia
This (b) (6)-year-old (b) (6) patient with potential underlying chronic renal insufficiency (initial SCr 2.4 mg/dL on (b) (6)), CAD and sinus bradycardia, was treated with terlipressin from (b) (6) Terlipressin was discontinued in anticipation of a liver transplantation. During his operation on (b) (6) (exact time not provided), (b) (6) developed ventricular tachycardia. (b) (6) ventricular tachycardia responded to pharmacologic therapy. Postoperatively, (b) (6) developed pneumonia (b) (6) that required several diagnostic fiberoptic bronchoscopies and prolonged intubation. (b) (6) also developed oliguric "acute" renal failure. (b) (6) renal function never recovered and he remained dialysis dependent.

(b) (6)
Pancreatitis; Biliary leak; Open surgical wound
This (b) (6)-year-old (b) (6) patient with recent respiratory failure from methicillin-resistant staph aureus pneumonia, metabolic coma from cirrhosis and medication, was started on terlipressin on (b) (6). Terlipressin was discontinued on (b) (6) after 12 doses/12mg total, when the patient required dialysis.

On (b) (6) (b) (6) received a liver transplant. Post-op on (b) (6) (b) (6) developed pancreatitis of moderate intensity. On (b) (6), (b) (6) was found to have a biliary leak, for which (b) (6) underwent a revision of hepaticojejunostomy with lysis of adhesions and a liver biopsy. After the surgical revision, (b) (6) had to be initiated on continuous venovenous hemodialysis to decrease bowel edema prior to closing the abdominal incision on (b) (6). The pancreatitis resolved on (b) (6). The patient remained hospitalized until (b) (6) death on (b) (6) due to "necrotizing bacterial pneumonia."

(b) (6)

Cyanosis

This (b) (6)-year-old (b) (6) patient was started on terlipressin on (b) (6) The patient developed blue fingers and toes on (b) (6) after the 7th dose of terlipressin and hence additional doses of terlipressin were initially held. Cyanosis apparently completed resolved and terlipressin was subsequently restarted on (b) (6) at 0.5 mg, half the initial dose. On that date, the peripheral cyanosis recurred post treatment with terlipressin, and hence terlipressin was permanently discontinued. Cyanosis completely resolved on (b) (6). The event was assessed as non-serious and of moderate intensity.

The patient received a liver transplant on (b) (6) and received dialysis beginning (b) (6). At the 180-day follow-up, the patient was alive and was not receiving dialysis.

(b) (6)

Lower extremity cellulites

This (b) (6)-year-old (b) (6) patient was started on terlipressin on (b) (6) Terlipressin was discontinued on (b) (6) after normalization of renal function. (b) (6) was discharged from the hospital on (b) (6)

On (b) (6), (b) (6) presented to the emergency room with shortness of breath and severe lower extremity cellulitis and was hospitalized for treatment with intravenous antibiotics. The lower extremity cellulitis resolved on (b) (6) The patient received a liver transplant on (b) (6). At the 180-day follow-up, the patient was alive and had not required dialysis.

(b) (6)

Renal failure

This (b) (6)-year-old (b) (6) patient was started on terlipressin on (b) (6) On (b) (6), terlipressin was discontinued after 15 doses, when (b) (6) received a liver transplant. (b) (6) was discharged from the hospital on (b) (6) with a creatinine of 1.8 mg/dL. After discharge, (b) (6) developed increasing ascites and lower extremity edema. On (b) (6), his creatinine increased to 2.9 mg/dL and (b) (6) was hospitalized for fluid management including treatment with albumin, diuresis and monitoring of renal function and electrolytes. The renal failure resolved on (b) (6) and (b) (6) was discharged home on (b) (6)

(b) (6) was alive at the 180-day follow-up and had not required dialysis at any time.

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PLACEBO

(b) (6)

Right caudate infarct

This (b) (6)-year-old (b) (6) patient was treated with placebo from (b) (6) Placebo was discontinued when (b) (6) was started on CVVH.

(b) (6) received a liver transplant on (b) (6). The postoperative course was complicated by an upper GI bleed and need for dialysis. On (b) (6), (b) (6) became unresponsive and developed a mild left-side paresis. The CT scan revealed a right caudate infarct. On neurological examination, (b) (6) demonstrated mutism and fascio-brachial-crural paresis consistent with a subacute lenticulostriate artery infarct. The event resolved on (b) (6)

(b) (6) was transferred to rehabilitation unit on (b) (6) at which time little residual effect was noted on neurological examination. (b) (6) was discharged on (b) (6)
At the 180-day follow-up, (b) (6) was alive and was not receiving dialysis.

(b) (6)
Upper gastrointestinal bleed
This (b) (6)-year-old (b) (6) patient with an unclear prior history of variceal hemorrhage, recent transjugular intrahepatic portosystemic shunt (TIPS) procedure on (b) (6), was treated with 4 doses of placebo from (b) (6). Placebo was discontinued when (b) (6) was initiated on dialysis.
On (b) (6) the patient developed bright red blood per rectum, for which (b) (6) received 2 units FFP and PRBC, respectively. (b) (6) INR was >9 on (b) (6), but information on vitamin K administration and prior hemoglobin was not provided. On (b) (6), the upper gastrointestinal bleed clinically resolved, and hematocrit stabilized at 26.6.
The patient received a liver transplant on (b) (6). At the 180-day follow-up, the patient was alive and was not receiving dialysis.

(b) (6)
Hemolytic anemia; Coagulopathy; Dehiscence abdominal wound
This (b) (6)-year-old (b) (6) patient with recent history endocarditis was treated with 37 mg of placebo from (b) (6). The placebo therapy, discontinued in preparation for a liver transplant scheduled on (b) (6), was not restarted after cancellation of that liver transplantation.

On (b) (6) (b) (6) developed constant oozing of blood following insertion of a central intravenous line, and required significant amount of blood products (24 units of platelets, 8 units fresh frozen plasma, 20 units of cryoprecipitate and 4 units of packed red blood cells). (b) (6) hematologic parameters were not provided.

On (b) (6) he ultimately received a liver transplant. On (b) (6) (b) (6) developed incisional abdominal wound infection. The wound cultures were positive for methicillin resistant staphylococcus aureus and pseudomonas. On (b) (6), (b) (6) also developed a dehiscence of wound with partial bowel evisceration. (b) (6) underwent a repair of abdominal wall evisceration and decompression of small bowel and removal of T-tube with repair of a choledochocholedochostomy leak. The coagulopathy resolved on (b) (6), but as of (b) (6) the hemolytic anemia was ongoing and the wound dehiscence had almost completely healed except for a small portion of the lower midline incision. At the 180-day follow-up, the patient was alive and had not required dialysis.

(b) (6)
Acute renal failure
This (b) (6)-year-old (b) (6) patient with evidence of chronic kidney disease (baseline SCr was 2.6 on (b) (6)) was treated with placebo from (b) (6) Placebo was discontinued when (b) (6) required dialysis. On (b) (6) (b) (6) received a liver transplant, but continued to receive dialysis post-transplantation. (b) (6) was last dialyzed on (b) (6) prior to discharge on (b) (6)

On (b) (6), (b) (6) was rehospitalized for anuria and further increases in WBC, creatinine and BUN levels from the previous day, the day of discharge. (b) (6) was found with elevated resistive indices and pelviectasis of the right kidney (abdominal ultrasound) and bilateral hydronephrosis and distended urinary bladder (CT of abdomen and pelvis). No information provided on whether these imaging abnormalities resolved without further therapy. (b) (6) was restarted on dialysis on (b) (6) (b) (6) was dialyzed on the day of discharge, and no ysis post discharge was planned.

Also on that hospitalization, (b) (6) developed fever and hypotension on (b) (6). A therapeutic paracentesis was performed on (b) (6) and blood cultures drawn on (b) (6) grew gram positive cocci in pairs and chains. Vancomycin, fluconazole and piperacillin/tazobactam were started on (b) (6), and hypotension and fever resolved the same day. The duration of antibiotic therapy not provided. (b) (6) was discharged home on (b) (6)

At the 180-day follow-up, (b) (6) was alive and was not receiving dialysis.

Reviewer comment: (b) (6) *delayed renal improvement after liver transplantation raises possibility of underlying intrinsic kidney disease and/or additional renal insult post liver transplantation. Potential causes include untreated bilateral hydronephrosis, sepsis, and/or high level of immunosuppressant which could be toxic to the kidneys. Taken together, I do not think "acute renal failure" should be attributed to placebo.*

(b) (6)
Hepatorenal syndrome; Hepatic encephalopathy
A (b) (6)-year-old (b) (6) patient with AH, mild hepatic encephalopathy, was treated with 24 mg of placebo from (b) (6). Placebo was discontinued due to treatment success. (b) (6) was discharged on (b) (6) with a creatinine of 1.3 mg/dL.

(b) (6) was rehospitalized due to an increase in SCr from 1.3 mg/dL (b) (6) to 2.8 mg/dL (b) (6). (b) (6) was retreated with 16 mg of placebo from (b) (6) with decrease in SCr to 1.2, and was discharged home on an unspecified date.

On (b) (6) 11 days after completing placebo therapy, the patient was rehospitalized with hepatic encephalopathy. SCr was 1.5 mg/dL and remained stable during this hospitalization.

At the 180-day follow-up, the patient was alive and had not received a liver transplant nor had (b) (6) required dialysis.

Reviewer comments: hepatorenal syndrome was the condition under study, and should not be included as an adverse event due to placebo. Hepatic encephalopathy was part of the PMH, hence should not be included in the AE due to placebo unless it worsened.

(b) (6)
Post-operative intracranial hemorrhage; Melena; Respiratory distress
This (b) (6)-year-old (b) (6) patient with cirrhosis, esophageal variceal hemorrhage, thrombocytopenia, and anemia, (unknown baseline INR), was treated with a total of 35 mg placebo from (b) (6) (b) (6) renal failure progressed and (b) (6) was transferred to the ICU on (b) (6) for continuous veno-venous hemodialysis (CVVH).
On the evening of (b) (6), (b) (6) developed melena, with a decrease in hematocrit to 13. Vasopressors were required to maintain BP and multiple blood products were administered. An EGD revealed 1-2 esophageal varices. The melena resolved the same day.
Concurrent with the development of melena, (b) (6) also developed respiratory distress and was intubation till (b) (6)
On (b) (6), (b) (6) received a liver transplant. The intraoperative course was complicated by hypotension and extensive bleeding requiring infusion vasopressin and pressors. On (b) (6) the patient was noted to move only the left side in response to pain. CT scan revealed a left parietal bleed.
Subsequently, the patient was transferred to an inpatient rehabilitation program and had demonstrated progressive improvement in health. At the 180-day follow-up, the patient was alive and was not receiving dialysis.

(b) (6)
Right heart failure
This (b) (6)-year-old (b) (6) patient with reportedly asymptomatic mitral and tricuspid valve insufficiency was started on placebo on (b) (6) Placebo was discontinued after a total of 8mg on (b) (6) due to treatment failure.
On (b) (6) open-labeled intravenous terlipressin (commercial marketed product available in Germany) was administered at a dose of 1 mg four times per day. On (b) (6), 4 days after the discontinuation of placebo, and after unknown doses of terlipressin, (b) (6) developed distention of jugular veins bilaterally and was diagnosed with right heart failure. An echocardiogram revealed dilatation of the right heart and progression to grade 3 tricuspid insufficiency (baseline grade not provided). The open-label terlipressin was discontinued and (b) (6) was treated with intravenous nitroglycerin and furosemide.
On (b) (6), a cardiac catheterization was performed and revealed multiple high-grade stenotic lesions in the mid-distal third of the right coronary artery. (b) (6) was treated with balloon dilatation and placement of 3 non-drug eluting stents. The right heart failure resolved on (b) (6) after the coronary intervention.
(b) (6) received a liver transplant on (b) (6). At the 180-day follow-up on (b) (6), (b) (6) was alive and had not received dialysis.

6.2 Literature Review/References

A pubmed search conducted on October 20, 2009 with the terms “terlipressin” and “hepatorenal syndrome type I” and “double-blind” and limit the search to randomized controlled trial identified only one trial, the OT-0401 trial by the Terlipressin Study Group.

Seventeen studies with terlipressin in HRS, mostly uncontrolled, open-label studies, were only able to demonstrate a transient reduction in serum creatinine compared with either baseline SCr or controls. None of the studies reported a sustained improvement in SCr, or any morbidity or mortality benefit. For details, please see the review for NDA 22231 submission 3.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)

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/s/

NANCY N XU

11/04/2009

THIS REVIEW VERSION REPLACES THE PREVIOUS TWO VERSIONS DATED FEBRUARY 5, 2009 AND OCTOBER 20, 2009, RESPECTIVELY.
This version makes correction in the financial disclosure section, adds details in OT-0401 protocol, and corrects formatting and grammatical errors.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-231 (Lucassin; terlipressin for hepatorenal syndrome)

Sponsor: Orphan Therapeutics

Review date: 24 October 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-231
HFD-110/Park/Targum/Xu

This memo conveys the Division's recommendation not to approve terlipressin for reversal of hepatorenal syndrome (HRS).

Hepatorenal syndrome is characterized by cirrhosis and glomerular hypofiltration with no other renal pathology. It is thought to result from splanchnic vasodilation and renal vasoconstriction. HRS is often treated with vasodilators (like terlipressin) in the hope of improving net renal blood flow. HRS of rapid onset (HRS Type I) is, not surprisingly, associated with high mortality. The only definitive therapy is liver transplant.

The recommendations are based on reviews of CMC (Bhamidipati; 29 September 2009, 21 October 2009), Microbiology (Pawar; 1 October 2009), Pharmacology (Jagadeesh; 6 August 2009), QT (Balakrishnan; 4 September 2009), Clinical Pharmacology (Menon-Anderson; 27 August 2009), and medical/statistics (Xu and Lawrence; 12 February 2009, 20-21 October 2009). Most issues have been addressed in Dr. Targum's CDTL memo (7 October 2009). I summarize very briefly.

Terlipressin is a fully synthetic 12-amino acid analog of vasopressin with specificity for the V1 receptor. It is packaged as a lyophilized powder for reconstitution in 0.9% saline for bolus administration at 1 (b) (4) mg every 6 hours for up to 14 days (b) (4) (b) (4)

There are several unresolved, but hardly serious CMC issues. The Complete response letter will call for (1) methodology to confirm terlipressin's one disulfide bond, (2) assay for heavy metals in the drug substance, (3) methods for testing for residual solvents, (b) (4), and (4) stability across the range of (b) (4) There are no open microbiology issues.

Pharmacology (review based mainly on literature) confirms terlipressin's vasopressin-like activity and all known toxicity in animals appears to be attributable to exaggerated vasoconstrictor activity.

Terlipressin pharmacokinetics has been mostly studied in normal volunteers. It has a half-life (single phase) of about an hour, and it appears to be solely degraded by tissue proteases; it has no effect on CYPs in vitro. Sparse data in HRS patients show similar kinetics. Available data are inadequate to show a relationship between exposure and effects on serum creatinine.

No patients had anti-drug antibodies.

There was no QT study. ECGs during study OT-0401 (see below) revealed by obvious QT signal, but the medically unstable population and small sample size make this not particularly reassuring. Nevertheless, the QT team and I agree that this is probably

adequate work-up, considering the highly monitored clinical setting and the very short half-life.

There are two clinical studies.

Study OT-0401 was a double-blind study conducted mostly in the US in which subjects with HRS Type I were randomized to placebo (n=56) or terlipressin 1-2 mg q6h (n=56) for up to 14 days or until HRS reversal, defined by reduction of serum creatinine to <1.5 mg/dL, sustained at 40-56 hours, without dialysis or recurrence (creatinine >2.5 mg/dL) through 14 days. The pre-specified primary analysis excluded subjects having a liver transplant with the 14-day observation period ("MITT").

For the MITT analysis, the success rate was 14/48 on terlipressin and 7/44 on placebo (p=0.13). An ITT analysis gives rates of 14/56 and 7/56 for p=0.09.

The sponsor's post-hoc analysis of unconfirmed success (ignoring recurrence and death) gave rates (ITT) of 19/56 for terlipressin and 7/56 for placebo (p=0.008). The reviewers reapplied the rules for handling recurrence or death and get rates of 17/56 and 8/56 for p=0.07.

Thus, the only analysis even close to a one-trial standard for approval is the sponsor's post-hoc analysis. Neither the review team nor I think that this is compelling because of its post-hoc nature, its handling of recurrence and death, or the lack of confirmed or sustained reduction in serum creatinine.

The only other study is TAHRS, an open-label study conducted in Spain. It enrolled 46 of a planned 100 subjects with HRS Type I and II, and had significant crossover. Its primary end point was survival at 90 days, which was 26% in both groups. All survivors were transplant-free.

There are no obvious safety issues, but the extremely sick patient population and the small size of the development program give little reassurance.

Because the program seemed far from approval, it has not been discussed at an advisory committee.

The reviewers and I agree that another trial is needed to show a statistically significant effect on something prior to approval. The reviewers would like to see real clinical benefit demonstrated. Dr. Targum suggests possible end points of reduced need for dialysis or increased survival to liver transplant. While I agree that such a demonstration would be terrific, I do not believe that any such end point is feasible, given the small patient population and the scarcity of liver donors.

I had thought that a reasonable goal of therapy was to extend the opportunity for liver transplant, i.e., increase the time over which a patient is not rendered ineligible for liver transplant because of renal failure. Two things now give me pause in recommending such an end point. First, we are told that some people are advanced on the transplant list because of renal failure, rather than being dropped for it. Second, I note that in TAHRS, despite having a mix of HRS Types I and II, rather than all Type I like OT-0401, the only survivors at 90 days were subjects who never had a transplant. If both of those are true, I am at a loss to name a reasonable intermediate end point. Perhaps an advisory committee meeting on this would be useful.

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/s/

NORMAN L STOCKBRIDGE
10/30/2009

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology
OND IO
NDA: 22-231
Submission date: May 1, 2009
Drug: terlipressin
Sponsor: Orphan Therapeutics, LLC
Indication: hepatorenal syndrome (HRS) type 1
Reviewing Division: Division of Cardiovascular and Renal Products

Comments:

The nonclinical information for terlipressin appears adequate to support the proposed indication which generally involves relatively short duration treatment in seriously ill patients. The nonclinical studies showed significant toxicity. The toxicity appeared to be related to the expected pharmacologic effect mediated through activation of the vasopressin V_1 receptor.

Conclusions:

The pharmacology/toxicology reviewer indicated in his review that this NDA was "approvable". No additional nonclinical studies or requirements were suggested in the primary review. I have communicated with the pharm/tox supervisor and he believes the NDA can be approved from the pharm/tox perspective. The adverse findings observed in the nonclinical studies were significant but they were related to the expected pharmacologic effect of the compound and would not prevent approval if clinical benefit and safety were adequate. I agree that this NDA can be approved for the indication listed above and that no additional nonclinical studies are recommended at this time.

Labeling issues will be addressed at a later time when necessary.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)

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/s/

PAUL C BROWN
10/27/2009

Cross-Discipline Team Leader Review Memo

Date	October 6, 2009
From	Shari L. Targum, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	NDA # 22-231
Proprietary / Established (USAN) names	Lucassin®/Terlipressin
Dosage forms / strength	6 mL vials containing 1 mg lyophilized terlipressin diacetate pentahydrate, reconstituted with 5 mL 0.9% sterile saline.
Proposed Indication(s)	Treatment of hepatorenal syndrome type I
Recommended:	*Complete Response*

Purpose of Cross-Discipline Team Leader (CDTL) Review

This review is in concurrence with the medical-statistical recommendation that terlipressin not be approved for the treatment of hepatorenal syndrome (HRS) type 1.

To support approval, the sponsor submitted two clinical studies: one double-blind, placebo-controlled study in HRS type 1 patients with 180-day follow-up (OT-0401) and one open-label study in HRS 1 or HRS 2 patients with 90-day follow-up (TAHRS). Neither study "won" on its respective prespecified primary endpoint: incidence of treatment success (percentage of patients alive at Day 14 with at least 2 serum creatinine (SCr) values $\leq$ 1.5 mg/dL about 48 hours apart) (OT-0401) and survival at 90 days (TAHRS).

The sponsor presented a post-hoc analysis of the OT-0401 "incidence of HRS Reversal[1]," which showed a statistically significant difference between treatment groups. In TAHRS, the incidence of HRS reversal, a secondary endpoint, also showed a statistically significant difference between groups. No survival, hospitalization, or dialysis-related benefit was demonstrated in either study.

The sponsor may feel that a single creatinine $\leq$ 1.5 mg/dL, albeit "post-hoc," represents a clinical benefit. This reviewer concurs with the medical and clinical pharmacology reviewer that the relevance of a transient creatinine < 1.5 mg/dL in this condition is not clear, in the absence of any demonstrable clinical benefit.

The Agency has accepted renal function (e.g., reduced risk of increasing creatinine) as a benefit in other chronic conditions; during the terlipressin development program, the sponsor was advised to seek an endpoint of sustained reduction in serum creatinine rather than a transient value. In chronic renal disease, worsening renal function can serve as evidence of irreversible kidney damage with prognostic significance. However, hepatorenal syndrome

[1] HRS reversal was defined as the percentage of patients with at least one SCr value $\leq$ 1.5 mg/dL during treatment.

type I is an acute event and the analogy to chronic renal disease may not hold. Is it better to have a creatinine of 1.5 mg/dL, or 2.0 mg/dL, versus 2.5 or 3.0 mg/dl, when the need for dialysis is no different between groups and the survival remains low?

Some have suggested that a creatinine-based endpoint is a surrogate for other meaningful benefits (e.g., increased likelihood of liver transplant) that one might not be able to show if these trials cannot be adequately powered. The resulting creatinine endpoint will exist without the link to a clinical outcome, and conclusion of a benefit may be based on a belief that "patients will do better" if the creatinine is lower.

This reviewer would like to see the sponsor conduct an additional study that would demonstrate a clinically meaningful outcome other than creatinine, such as decreased need for dialysis. Or the sponsor could submit convincing evidence that terlipressin use will lead to an improved likelihood for liver transplant. In this seriously ill population, it would be unfortunate if there were no benefit other than "the numbers look better" --particularly if there are safety/tolerability issues. It would also be unfortunate if drugs could not be developed that could provide benefit for these patients.

Since hepatorenal syndrome type 1 is an "orphan" indication, it may be difficult to generate a sample size adequate enough to show statistically significant and clinically meaningful benefits, especially if the "effect size" is modest. Furthermore, it may be difficult to address whether baseline imbalances have affected results in a single small study in a sick, unstable population. Results with favorable, but not statistically significant, "trends" may lead one to wonder whether the study is simply underpowered (the result could be real), or whether the result is a "play of chance." Even with these obstacles, however, one needs some reasonable evidence of effectiveness.

Other issues include:

1. Reliance on a "responder analysis" (incidence of hepatorenal syndrome reversal based on a single arbitrary creatinine value);
2. Potential confounding of any statistically significant difference in creatinine as a result of differences in fluid/albumin administration or imbalances in the entry population (i.e., inclusion of potentially reversible causes of renal dysfunction);
3. The presence of baseline imbalances in both studies (OT-0401 and TAHRS). It is not clear whether these baseline imbalances confounded any statistically significant findings.
4. Since few patients completed 14 days of therapy in OT-0401, the analysis of creatinine data becomes problematic with regard to handling of dropouts and missing creatinine results.
5. Some of the creatinine analyses in OT-0401 were confounded by inclusion of values from patients receiving dialysis and/or transplant.
6. In OT-0401, continuing treatment after achieving treatment success is at the discretion of the investigator. As a result, there is variable availability of on-treatment SCr for analysis after treatment success.

7. The question of appropriate dosing and dose interval does not appear to have been adequately explored. In addition, the submission did not explore an optimal time and algorithm for dose titration.
8. There is some suggestion in the literature that albumin may have some effect in hepatorenal syndrome; consequently, the relationship between terlipressin and albumin has not been well-characterized.

1. Introduction to Review

This review is based, in part, on the primary reviews of:

- Chemistry (Shastri P. Bhamidipati, Ramesh Sood), 9/29/09
- Product Quality Microbiology (Vinayak B. Pawar, Stephen E. Langille), 10/1/09
- Pharmacology and Toxicology (Gowra Jagadeesh, Charles Resnick) 8/6/09
- Clinical Pharmacology and Biopharmaceutics (Divya Menon-Andersen, Pravin R. Jadhav, Rajanikanth Madabushi), 8/27/09
- QT (Suchitra Balakrishnan), 9/4/08
- Clinical and Statistical (Nancy Xu and John Lawrence),
- Immunogenicity (Melinda J. Bauerlien, Michael A. Phelan, Daniela I. Verthelyi), 9/16/09
- Division of Medication Error Prevention and Analysis (Anne Crandall), 8/13/09

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Hepatorenal syndrome (HRS) describes the development of renal dysfunction in patients with end-stage cirrhosis in the absence of any other cause of renal pathology. One proposed mechanism is vasoconstriction of the renal circulation due to marked splanchnic vasodilatation, leading to reduction in effective arterial volume.

Two types of HRS exist:

Type 1—rapid and progressive impairment of renal function defined by doubling of the initial serum creatinine level to > 2.5 mg/dL or 50% reduction of the initial 24-hour creatinine clearance to < 20 mL/min in less than 2 weeks.

Type 2—impairment in renal function leading to serum creatinine level > 1.5 mg/dL that does not meet the criteria for type 1.[2]

According to the sponsor, the differences between types 1 and 2 are "arbitrary." However, the natural history appears to be different between the two types; median survival in type 2 HRS is longer than in type 1 HRS.[3,4] The reader is also referred to a more detailed discussion in the primary medical-statistical review (primary medical-statistical review, section 2.2).

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[2] Source: Harrison's Principals of Internal Medicine, among others.

[3] Arroyo V et. al. Definition and Diagnostic Criteria of Refractory Ascites and Hepatorenal Syndrome in Cirrhosis. *Hepatology 1996; 23: 164-176.*

The current treatment of choice for HRS patients is liver transplantation. However: 1. patients with HRS 1 may not survive long enough to receive a transplant; and 2. patients with HRS who receive transplants may have higher in-hospital mortality than those without HRS.[5] There is no U.S.-approved pharmacologic therapy for HRS.

Terlipressin is a vasopressin analogue and systemic vasoconstrictor with effects mediated via vasopressin V_1 receptors. The hypothesized mechanism of action is an increase in effective arterial volume, leading to an increase in mean arterial pressure and normalization of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system) resulting in increased renal perfusion and renal function.

According to the sponsor, terlipressin has been recently approved, based on literature reports, for the treatment in HRS type 1 in France, Ireland and South Korea[6]. In addition, terlipressin is approved in several European countries for the treatment of esophageal variceal hemorrhage (EVH); the approved EVH dose is 1-2 mg intravenous bolus every 4-6 hours up to 72 hours.

Table 1. Regulatory History: NDA 22231

Date	Milestone	Discussion points
1/22/04	Pre-IND meeting	• The sponsor should verify that HRS type I definition is identical to the historical definition when using historical data to support approval. • The sponsor was encouraged to look at sample size, include an interim analysis, and make adjustments accordingly. • A single clinical trial should be robust since it might not provide sufficient benefit to support approval. • Follow-up assessments of creatinine and liver function would be needed (e.g., out to 60 days) • Other recommendations: Six-month mortality data, assessment of MELD score and encephalopathy, studying more than one dose, analyzing the primary endpoint using MITT and ITT populations.
3/17/04	Pre-IND teleconference	• Concern about mandating background albumin therapy; albumin is not approved in this indication. • Concern about alpha = 0.05 too high given the need for this single trial to be highly convincing; if the literature describes a different population and/or were difficult to interpret, then an alpha $\leq$ 0.01 was suggested.
3/31/04	IND filed -- study OT-0401 allowed to proceed.	
10/29/04	Orphan drug designation granted.	
4/5/05	Fast-track status granted.	
11/22/06	Pre-NDA meeting	• The sponsor's findings are not compelling; the primary endpoint failed to show statistical significance at $p < 0.05$. The sponsor

[4] An oft-quoted statistic in the literature is that the median survival is 2 weeks and 6 months for types 1 and 2 HRS, respectively.

[5] The effect of terlipressin on in-hospital mortality in transplant patients was not explored in this application.

[6] Per French labeling, the recommended dose in HRS type 1 is 3-4 mg administered 3-4 times/24 hours until there is at least 30% reduction in creatinine level; the average duration of treatment is 10 days.

		claimed that they were "too ambitious in the design of their primary endpoint, but are willing to conduct another study, taking into consideration guidance from the Agency on study design." • The Agency agreed that "HRS reversal was a reasonable endpoint, but it cannot be defined as a one-time SCr improvement that then goes away." • The Agency agreed to a rolling review.
5/4/09	Complete NDA received	
2/6/09	First discipline review letter (DRL) sent	• Single pivotal study demonstrated a modest and transient effect on improving SCr without sustained improvement. • More treatment-emergent adverse events and a slightly higher on-treatment mortality rate observed in terlipressin-treated patients compared to placebo. Higher adverse event and mortality rates in the terlipressin arm were also seen in TAHRS. • Primary endpoint changed post-trial completion. • Secondary endpoint analyses were different from the pre-specified analyses. • Incomplete information (e.g., verification of HRS 1 diagnosis, SCr values excluded from analyses, actual death dates, adverse events not included in safety dataset). • Frequent protocol amendments made after significant amount of data collection; • Dose, duration of therapy and influence of co-interventions not established.
7/2/09	Letter to sponsor granting priority review.	
7/27/09	Teleconference with sponsor	• Sponsor notified of Agency decision to cancel Advisory Committee meeting scheduled for October, 2009.
8/6/09	Second DRL sent	• Further discussion on whether repeated measures analysis is appropriate; whether baseline imbalances in creatinine account for lack of survival benefit; whether a placebo patient (b) (6) should have been excluded from HRS reversal analysis; statistical analysis for HRS reversal.
9/3/09	Meeting with sponsor	• FDA still agreed that "HRS reversal is a reasonable endpoint, but cannot be defined as a one-time measurement that goes away." • Too many subjects had dialysis, underwent transplant, died, or had missing SCr for an analysis of HRS reversal without recurrence by Day 30; however, if this were a prespecifed primary endpoint with little missing data, this might be a good endpoint. • The sponsor was encouraged to conduct another study in HRS 1, collecting daily SCr even if patients discontinue. The sponsor could use the existing pre-specified primary endpoint, Treatment Success at Day 14; or the sponsor could demonstrate a more compelling benefit for harder clinical outcomes.

3. CMC/Microbiology/Device

The CMC reviewer is not recommending approval because of pending CMC issues related to drug product characterization and analytical procedures. Based on the review of stability data,

the recommended shelf-life for the product is limited to (b) (4) At the time of this writing, the Agency is awaiting a response to an information request letter to the sponsor listing nine issues (9/22/2009). Deficiencies cited in the CMC review are listed in section 3.2. An ONDQA Division memo is pending at this time.

No deficiencies were observed in the assessment of product quality microbiology.

3.1. General product quality considerations

Drug Substance: Terlipressin is a 12-residue synthetic peptide with the primary sequence of Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly with a disulfide bond. The drug substance is synthesized by (b) (4) and characterized by physical, chemical and analytical methods to establish the structure. The manufacturing process includes appropriate in-process controls and has been adequately characterized. The analytical procedures for release of drug substance have been adequately described and validated.

The specification for the drug substance, however, did not include (b) (4) (b) (4)

Drug Product: The drug product is a preservative-free sterile lyophilized powder and the formulation contains terlipressin at 0.85 mg as free base; mannitol, USP (b) (4) glacial acetic acid, USP and/or sodium hydroxide, NF (used for pH adjustment) and water for injection USP. Lucassin® (terlipressin) for injection is packaged in 6 mL clear glass vial and will be marketed in only one strength (0.85 mg/vial) for single use. The drug product should be reconstituted with only 0.9% Sodium Chloride solution for injection prior to administration. The proposed drug product specification has met the quality requirements for parenteral products.
However, the (b) (4) of the lyophilized product have not been adequately characterized. In addition, data to support use of reconstituted product are inadequate (b) (4) (b) (4)

Impurity profile: There has been inadequate characterization of impurities in drug product. The main impurity detected was the (b) (4) impurity, (b) (4) which has been characterized; however, there are two additional impurities: (b) (4) and an (b) (4) (b) (4) The sponsor has been asked to provide structural characterization information for (b) (4)

Stability and shelf-life: Stability data to support the use of reconstituted solution for administration have been determined to be inadequate due (b) (4) Based on stability data and results from a method comparison study, the CMC reviewer has concluded that a shelf life beyond (b) (4) cannot be recommended without additional information justifying the use of supporting stability data.

3.1.1. Facilities review/inspection

An inspection of two domestic facilities is pending at this writing; there is no final report available.

3.2. Other notable issues

Four deficiencies from the CMC review are listed below and await resolution:

(b) (4)

2. The specification for drug substance should include testing for heavy metals to ensure that every batch meets the USP <231> requirement.

3. The analytical method intended for quantitation of residual solvents in the drug substance is inferior to USP method based on LOD and LOQ values in the validation report. Additionally, data provided in attachment 2 in response to the information request letter are inconsistent with the LOD and LOQ values per validated method.

4. Based on the results provided for three drug substance lots, the specification for drug substance should include testing for (b) (4)

4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

In animals and humans, terlipressin is metabolically converted to lysine vasopressin; both are rapidly eliminated, necessitating frequent dosing. The mean half-life estimates for terlipressin and lysine vasopressin in animals were about 0.2 hr and 2 hrs, respectively, similar to that observed in HRS patients.

Based on *in vitro* data, Terlipressin had no significant effect on human red cell fragility and produced no hemolysis. In addition, terlipressin did not inhibit or induce activity in any of the human cytochrome P450 isozyme studies.

Single-dose intravenous toxicity studies were performed in mice and rats, and repeat intravenous toxicity studies were conducted in rats and dogs. At the terlipressin dose used to

treat HRS patients, the V_1 receptor-mediated vasoconstrictor activity appeared to be the pharmacodynamic mechanism responsible for its clinical activity, as well as the observed adverse effects. The major organ system affected by terlipressin in both species was the kidney. Dose-related injection site inflammation was also observed.

Twenty-eight day studies in rats and dogs showed a moderate decrease in body weight gain in males (relative to controls), a non-dose-dependent decrease in mean absolute kidney weight in male rats and dogs at all doses, and dose-related renal histopathologic changes (such as multifocal chronic cortical nephritis); in rats, but not dogs, there was a decrease in testes weight at 0.5 mg/kg/day terlipressin with seminiferous tubular degeneration that was absent in control animals and not resolved by the end of the 2 week recovery period.

Deaths in rats (MTD 2 mg/kg) appeared to be due to severe vasoconstriction resulting in reduced perfusion, pulmonary congestion and inflammation of the lungs; most of these deaths were dose-dependent and occurred on the first day of dosing, and splitting the daily dose into two decreased the intensity and incidence of clinical signs and mortality.

From comparisons based on body surface area-adjusted dose levels, the lowest terlipressin adverse effect dose level in rats (LOAEL) was about 1-2 times that studied in HRS patients; in dogs, the LOAEL dose was 0.7-1.5 times that studied in HRS patients. Little safety margin was demonstrated; however, based on past clinical experience, the pharmacologist has suggested that terlipressin can be used safety for the treatment of HRS.

4.2. Carcinogenicity

Terlipressin has no mutagenic or clastogenic activity. No carcinogenicity studies were performed.

4.3. Reproductive toxicology

Based on the literature, there is evidence of human fetal risk due to increased uterine contractility and reduced blood flow to placenta and uterus.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Terlipressin is formulated for intravenous administration as a slow bolus (~2 minutes) injection. The proposed starting dose is 1mg/kg every six hours; the dose may be doubled to (b) (4) mg/kg after three days, if serum creatinine does not decrease by 30% from the baseline value. Treatment is to be discontinued if any of the following occurs: 1. (b) (4) days after SCr < 1.5 mg/dL is achieved; (b) (4) (b) (4) 4. after 14 days of administration.

The pharmacokinetics (PK) of terlipressin in HRS type 1 patients were characterized by population PK analysis of sparse sampling in OT-0401. The multiple-dose estimated clearance was 32.3 L/h (inter-subject variability 68%) and the central compartment volume of distribution was 37 L. The terminal elimination half-life was about 1 hour.
The PK of terlipressin in HRS type 1 patients appeared to be similar to that observed in healthy subjects. Single-dose PK were not evaluated in this NDA. In a previously reported study in healthy subjects, terlipressin clearance was 41.5 L/h following a single IV dose; mean elimination half-life was 1 hour.

Based on data from healthy subjects, plasma concentrations increase proportionately with dose.

A relationship between terlipressin exposure and change in serum creatinine was not apparent from the data collected in OT-0401. Exposure-response relationships for death, all serious adverse events (SAE), organ failure, transjugular intrahepatic portosystemic shunt (TIPS), treatment-related SAE were also explored graphically; no relationships were apparent. However, the OT-0401 exposure-response data were limited; all pharmacokinetic measurements were made after study day 3; twenty-two of 56 patients randomized to terlipressin discontinued from the study before day 3.

None of the terlipressin-treated patients developed antibodies to the product; however, please see immunology review for a description of assay deficiencies (below).

5.2. Drug-drug interactions

No in vivo drug-drug interactions are expected, given the pathway of elimination (below, section 5.3) and lack of effect on the cytochrome system.

5.3. Pathway of Elimination

Terlipressin is degraded by tissue peptideases (not expected to be different between healthy subjects and HRS type 1 patients). The active metabolite, lys-vasopressin, is formed by stepwise cleavage of the terminal glycyl residues of terlipressin; lys-vasopressin undergoes rapid degradation via C-, N-terminus and disulfide bond cleavage.
The elimination half-life of terlipressin and its active metabolite lys-vasopressin is about 1 hour and 6 minutes, respectively. Less than 1% of terlipressin and < 0.1% of lys-vasopressin are eliminated in urine.

Based on available OT-0104 data, no significant effect of weight, gender, age, creatinine clearance, Child-Pugh score, liver enzymes or total bilirubin were observed on terlipressin exposure.

5.4. Thorough QT study or other QT assessment

Using study OT-0401, which was not designed or powered as a “thorough QT study”, the sponsor submitted an analysis of paired electrocardiograms (ECGs) at baseline and on study

days when peak drug concentrations were expected (Days 3 and 7) and end of treatment (EOT) or Day 14; in addition, plasma samples were used to develop a PK/PD model of terlipressin plasma concentrations and corrected QT (QTc) intervals.

The QT review team was unable to come to any conclusions regarding QT effect of terlipressin due to limitations of design, acquisition of ECGs, time averaged statistical analyses and confounding due to patient population. Several patients had baseline ECG abnormalities and almost 50% of patients had no ECGs on Day 7 and 14. A small numerical trend (p= ns) toward more QTcF outliers was observed in the terlipressin-treated group compared to placebo (Table 5-10, QT-IRT review, page 6, reproduced below). Noting that terlipressin will be administered in an inpatient setting, the team suggested that telemetry could be recommended if not already in place. In addition, caution could be advised with respect to concomitant hypokalemia, hypomagnesemia and QT-prolonging medications.

Table 5-10. Incidence of Outlier QT/QTc Interval Values (Worst Scenario)

Outlier Group	Terlipressin (N=41)	Placebo (N=48)	P-value
QT Interval			
Change >30 msec	13 (31.7)	6 (12.5)	0.028
Change of 30–60 msec	8 (19.5)	6 (12.5)	0.365
Change >60 msec	5 (12.2)	0 (0)	0.018
New >500 msec	1 (2.4)	0 (0)	0.461
QTcB Interval			
Change >30 msec	12 (29.3)	8 (16.7)	0.156
Change of 30–60 msec	10 (24.4)	7 (14.6)	0.241
Change >60 msec	2 (4.9)	1 (2.1)	0.593
New >500 msec	6 (15.8)	4 (9.8)	0.509
QTcF Interval			
Change >30 msec	10 (24.4)	5 (10.4)	0.079
Change of 30–60 msec	6 (14.6)	4 (8.3)	0.503
Change >60 msec	4 (9.8)	1 (2.1)	0.176
New >500 msec	2 (4.9)	0 (0)	0.214

Source: Tables 1.8.0 and 1.9.0 (16 Jan 2007).

5.5. Other notable issues *(resolved or outstanding)*

The NDA is acceptable from a clinical pharmacology perspective, provided that an agreement is reached between the sponsor and the Agency regarding labeling.

The clinical pharmacology reviewer noted that a larger number of terlipressin-treated patients than placebo-treated patients had a decrease from baseline in SCr. Fifteen terlipressin-treated patients vs. 6 placebo-treated patients had SCr < 1.5 mg/dL by study Day 7. However, the relevance of this observed decrease in SCr < 1.5 mg/dL is not clear, since the number of deaths was similar between terlipressin and placebo; the number of patients receiving liver transplant or who met criteria for dialysis was also similar between terlipressin and placebo.

Study OT-0401 limitations noted by the clinical pharmacology reviewer were as follows:

1. Patients in OT-0401 were treated for variable number of days after SCr had reached < 1.5 mg/dL, confounding interpretation of the observed change in SCr.
2. Six terlipressin-treated patients had baseline SCr > 7 mg/dL, creating a baseline imbalance.

3. PK sampling was performed after study day 3, after 22 terlipressin patients had discontinued treatment.

For clinical pharmacology recommendations, please see section 13.2.

6. Clinical Microbiology

Clinical microbiology is not applicable to this NDA. A product quality microbiology review is summarized in the CMC section.

7. Clinical/Statistical

Agreements/discussion/disagreements with the sponsor

Please see Table 1 for Regulatory History and prior discussions/agreements.

The Agency agreed that the sponsor could "win" with a sustained reduction in creatinine, if results were robust. However, the sponsor was told that a one time reduction in creatinine that "went away" did not constitute adequate evidence of effectiveness.

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The basis for dosing and dosing interval selection in OT-0104 appears based on literature (2-6 mg/day) and discussion with experts in the field. The sponsor did not submit exploration of dose range or dosing interval.

7.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

Study OT-0401 was a randomized, placebo-controlled, double-blind, 112-patient, 35-site study. Eligible HRS type 1 patients were randomized to receive terlipressin or placebo, stratified by the presence or absence of alcoholic hepatitis. Patients received up to 14 days of study drug and then returned to the clinic on Days 14, 30 and 60; telephone follow-up was conducted on Days 90 and 180. The study included a steering committee and a DSMB.

Since hepatorenal syndrome type 1 is a diagnosis of exclusion, a screening log was provided to capture data on potential patients; however, use of this log varied among the sites. It is not clear how many enrolled patients did not meet criteria for HRS type 1 and whether imbalances existed across treatment groups.

Eligible patients had chronic or acute liver disease and rapidly progressive reduction in renal function (SCr doubling to at least 2.5 mg/dL in < 2 weeks prior to HRS diagnosis, or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 mL/min); proteinuria < 500 mg/day and no decrease of SCr to 1.5 mg/dL or less or increase in creatinine clearance to at least 40 mL/min after diuretic withdrawal and plasma volume expansion with 1.5 L isotonic saline;
Patients were given 1 mg study drug every 6 hours; if SCr had not decreased by at least 30% from baseline after 3 days, the dose was increased to 2 mg Q6 hours (8 mg/day).[7] Dosing was terminated for: treatment success (at the discretion of investigator), treatment failure (met criteria for dialysis or SCr ≥ baseline at Day 7 or later), liver transplantation, study withdrawal for other reasons, or completion of 14 days of therapy. Patients with partial response[8] who developed HRS recurrence during the follow-up period were eligible for retreatment for up to 14 additional days.[9] Renal function was monitored via SCr at baseline and daily until treatment termination; dialysis represented 'treatment failure'.

The "incidence of Treatment Success at Day 14" was the percentage of patients alive at Day 14 who demonstrated SCr ≤ 1.5 mg/dL on ≥ 2 measurements 48 hours apart, without dialysis or HRS recurrence, divided by total # patients in the MITT population at Day 14. Deaths/early withdrawals were included in the denominator but not identified as having treatment success. "Incidence of HRS reversal", a post-hoc analysis,[10] was defined as the number of patients who demonstrated at least one SCr ≤ 1.5 mg/dL during treatment without intervening dialysis/liver transplantation divided by the total # patients in the ITT population multiplied by 100.

There were five secondary and seven tertiary endpoints. Please see the primary medical-statistical review for further discussion of these endpoints.

The sample size calculations were based on 90 patients in the MITT population and a 95% power to detect a 30% difference in the primary efficacy endpoint between terlipressin (35%) and placebo (5%). The analyses of treatment success at Day 14 were based on the MITT population (ITT population who did not receive a liver transplant) as the primary analysis population.

Results: Fifty-six patients in each treatment group were randomized and included in the ITT analysis. Eight terlipressin and 12 placebo patients underwent liver transplant and were excluded from the MITT analysis.

Only eleven patients (19.6%) on terlipressin and 5 (8.9%) on placebo received 14 days of study treatment. Eighteen (32%) terlipressin and 23 (41%) placebo patients were deemed to have treatment failure (including lack of improvement, death and dialysis); and 10 terlipressin and 17 placebo patients were terminated early (there was no significant difference in

[7] Thirteen terlipressin patients received at least one 2 mg dose.
[8] Partial response was defined as number of patients alive with SCr above 1.5 mg/dl but > 50% reduction from baseline without dialysis or HRS recurrence divided by total number of patients randomized. This number was then multiplied by 100.
[9] According to the dataset SCR.XPT, only two patients (1 placebo, 1 terlipressin) were retreated.
[10] In a teleconference on 7/27/09, the sponsor concurred that HRS reversal was a post-hoc analysis.

withdrawals due to AE). Six terlipressin and 7 placebo patients were withdrawn and transferred to palliative care.

Twenty-two (39%) terlipressin patients and 17 (30%) placebo patients received ≤ 3 days of treatment.

The mean age of the study population was about 51-53 years; this study population was mostly male (about 70-73%) and Caucasian (about 90%). About 91% had a history of cirrhosis; about half due to alcohol; about 34-39% due to hepatitis C. The median Child-Pugh score was 12.0 and the median MELD score was 34.0. A higher number of subjects on terlipressin had baseline serum creatinine > 7.0 (6 terlipressin vs. 0 placebo, see Figures below). The two groups had mild baseline hyponatremia with mean sodium 130.55 (terlipressin) and 132.39 (placebo); INR for both groups was elevated at 2.25 (terlipressin) and 2.3 (placebo). Most patients were Child-Pugh class C (76.8-78.6%).

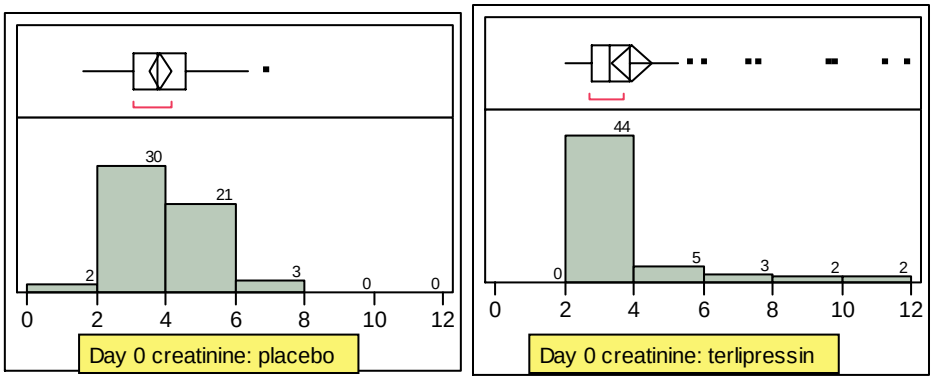

Figure 1. Histogram of the distribution of Day 0 creatinines for terlipressin and placebo: subject counts displayed on bars (1. More outliers in the group randomized to terlipressin; 2. Distribution of baseline creatinine appears different between two groups).

Forty-nine (87.5%) patients in each treatment group received concomitant albumin. The mean albumin exposure was 6.0 days (terlipressin) and 5.0 days (placebo); the mean total exposure was 294.44 g for terlipressin and 240.82 g for placebo and the mean daily exposure was 48.20 g for terlipressin and 45.63 g for placebo.
It is not clear whether these differences in albumin exposure confound any significant results seen between treatment groups.

As noted in the medical-statistical review, the prespecified primary endpoint showed a favorable "lean" toward terlipressin that was not statistically significant.

Table 2. OT-0401: Prespecified primary endpoint, incidence of treatment success (source: medical-statistical review, Table 8, page 21)

Incidence of treatment success	Terlipressin	Placebo	p-value
	14/48 (29%)	7/44 (16%)	0.131 (MITT)[a,b]
	14/56 (25%)	7/56 (12.5%)	0.093 (ITT) [a]

[a]Analysis by CMH test for general association adjusted for AH.
[b] Pre-specified primary analysis. The Modified intention to treat (MITT) population excludes patients who received liver transplant prior to Day 14.

In a post-hoc analysis, the sponsor observed a statistically significant difference in patients with HRS reversal. The sponsor defined HRS Reversal as having "any SCr values *before* the last non-missing dose date in a patient who had not had a transplant or dialysis, less than or equal to 1.5 mg/dL."

The medical-statistical reviewers performed an analysis, including a placebo patient with a qualifying SCr $\leq$ 1.5 mg/dL prior to transplant and excluding 2 terlipressin patients who died (b) (6) or had HRS recurrence (b) (6) and obtained results that differed slightly from the sponsor and were not statistically significant between groups:

Table 3. Post-hoc analysis of HRS Reversal

	Terlipressin n/N (%)	Placebo Control n/N (%)	P value 95% CI
Sponsor ITT	19/56 (34%)	7/56 (13%)	0.008
FDA ITT	17/56 (30%)	8/56 (14%)	0.068[a]
MITT	17/48 (35%)	7/44 (16%)	0.060[b]

[a, b] 2-tailed Fisher exact test
Source: Medical-statistical reviewers, mid-cycle presentation

An analysis of HRS reversal without recurrence to Day 30 showed results that were not statistically significant, although the "lean" (albeit with small numbers) is favorable toward terlipressin:

Table 4. OT-0401: HRS Reversal on treatment without recurrence to Day 30

Terlipressin N=56 n (%)	Placebo N=56 n (%)	p-value
10 (17.9)	5 (10.7)	0.27 (ITT)

Source: Medical-statistical reviewers, Discipline Review letter (8/27/09)

In another post-hoc analysis, the sponsor notes that patients with treatment success/HRS reversal at Day 14 had a mean baseline Child-Pugh score of about 11; baseline SCr median 3.2 (range 2.1-5.6) and mean baseline MELD score of about 31 (e.g., MELD and Child-Pugh scores lower than the median baseline scores). One implication of this analysis is that "less sick" patients are more likely to respond.

Of the secondary efficacy endpoints (exploratory, since the primary endpoint was not significantly different between treatments), the sponsor claimed that terlipressin-treated patients showed a statistically significant reduction in SCr from baseline to Day 14 (MITT) relative to placebo (0.7 mg/dL reduction with terlipressin vs. 0.1 mg/dl rise with placebo, p=0.015, repeated measures analysis); results were similar in the ITT analysis. However, the primary reviewers repeated this analysis excluding patients who received dialysis or transplant and using the original prespecified analysis (ANCOVA) and these results were not statistically significant (below).

Table 5. Mean change in SCr from Day 0 to Day 14 (OC), excluding patients who received dialysis of transplantation prior to Day 14 (Source: medical-statistical review, Table 11, page 22)

Study	Terlipressin (n=23) Mean (standard deviation)	Placebo Control (n=15) Mean (standard deviation)	P value
OT-0401	-1.59 (1.22)	-1.02 (1.94)	0.28[a]MITT

[a]Analysis by FDA using ANCOVA.

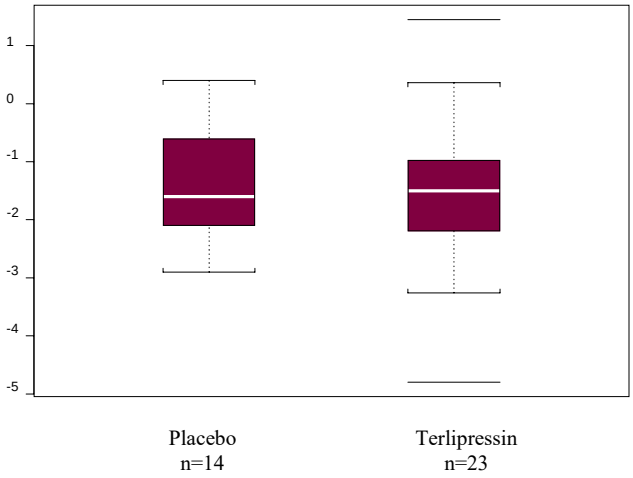

Figure 1. FDA Analysis: median change in SCr from Day 0 to Day 14 in patients who did not receive dialysis or transplant (source: medical-statistical review).

The sponsor also submitted a repeated measured analysis of the change from baseline in serum creatinine from Study Day 1 to Day 14 regardless of baseline or dialysis status. This reviewer agrees with the primary medical-statistical reviewers that inclusion of creatinine measurements post-dialysis and post-transplantation confound any interpretation of this analysis.

The other secondary efficacy variables did not show statistically significant differences between treatment groups.

Of the seven tertiary endpoints, the only statistically significant difference between groups was seen in the MELD score, which showed a statistically significant decrease in the overall repeated measures LS mean change from baseline through Day 14 with terlipressin-treated patients vs. placebo:

Table 6. Repeated Measures Analysis of Change from baseline in MELD study by Study Day through Day 14 using Observed Cases (MITT at Day 14) (source: sponsor, Table 4.2.18)

Time point	Terlipressin N LS Mean (SE)	Placebo N LS Mean (SE)	Terlipressin vs. Placebo LS Mean[a] (SE)	P-value[b]
Day 1	36 -0.2 (0.32)	30 0.5 (0.34)	-0.7 (0.47)	0.115
Day 3	32 -2.6 (0.67)	27 -0.4 (0.72)	-2.2 (0.98)	0.029
Day 7	18 -4.3 (0.85)	11 -1.1 (0.98)	-3.2 (1.30)	0.016
Day 14	25 -4.4 (0.92)	18 -2.2 (1.06)	-2.2 (1.40)	0.119
Overall	-2.9 (0.57)	-0.8 (0.63)	-2.1 (0.84)	0.016

a: Calculated as the Terlipressin LS Mean Change from baseline minus placebo LS Mean change from baseline.
b: From Repeated Measures ANOVA as implemented in Proc Mixed with factors Treatment, Day, Strata (alcoholic hepatitis present or not), Treatment by Day, Treatment by Strata (if significant), and Repeated statement with factor Patient nested in Strata. Treatment p-values within Day are obtained from the Treatment by Day interaction, whereas the overall treatment p-value is obtained from the overall treatment comparison.
Note: Model uses unstructured covariance matrix and maximum likelihood estimation.
Cross Reference: Data Listings 12 and 25

The calculation of MELD scores incorporates serum creatinine, total bilirubin, and INR.

MELD scores decreased in patients on placebo as well as terlipressin and the meaningfulness of a significant change in MELD score is not clear. In addition, it is not clear whether the results would be different if the missing data (see N, Day 3 and Day 7) were handled differently.

No significant differences between groups were seen in overall or transplant-free survival up to 14, 30, 90 or 180 Days.

In summary, OT-0401 failed to win on its prespecified primary endpoint. The sponsor has presented HRS reversal, a post-hoc analysis, to support their claim of benefit in HRS type 1. The FDA medical-statistical reviewers obtained results that differed slightly from the sponsor but were not statistically significant. Given the various issues with this small single study (missing data, potential confounding, post-hoc analyses, uncertain clinical benefit), this reviewer does not find the efficacy results compelling.

TAHRS was a randomized, open-label study conducted at 9 sites in Spain (2002-2006).

The study enrolled HRS types 1 and 2 (stratified by type). Patients were randomized to receive terlipressin plus albumin or albumin alone. Unlike OT-0401, the original protocol specified a lower initial terlipressin dosing of 0.5 mg every 4 hours with criteria for dose escalation. In April, 2003, the initial dose was increased to 1 mg every 4 hours. Albumin was administered to both groups as 1 g/kg on the first day and 40 g/day on subsequent days, to maintain a central venous pressure 10-15 cm water. Patients were to be followed for up to 90 days.

In the original protocol, 100 patients were planned over 36 months. The expected survival difference of 30% (5% in the albumin control group and 35% in patients treated with terlipressin + albumin) was based on pilot studies with terlipressin and ornipressin. However, this study was terminated, after 4 years of enrollment (67 screened and 46 randomized, 23 to each group), after an interim analysis showed a 3 month survival difference of 8% between the two groups (p=NS). Based on this interim analysis, the estimated sample size to demonstrate a significant difference was 431/group.

The primary medical reviewer has stated that the study was terminated due to the observed higher mortality rate in the terlipressin arm. However, the interim analysis was prespecified

and the decision to stop could have occurred due to concerns about sample size. As this was an open-label study, this reviewer cannot tell whether safety concerns played into the decision to stop TAHRS.

The primary endpoint was survival at 3 months. Secondary endpoints were survival at one month and reversal of hepatorenal syndrome (a decrease in serum creatinine to $\leq$ 1.5 mg/dL during treatment). A partial response was defined as decrease in serum creatinine during treatment $\geq$ 50% baseline, but not to < 1.5 mg/dL. A relapse was defined as an increase in serum creatinine > 2.6 mg/dL during the study period (including the 3 month follow-up) after exclusion of other causes of renal insufficiency and if the HRS criteria are met; relapse applies only to patients with a prior complete response.
A protocol amendment (April 2003) allowed patients randomized to albumin to crossover to terlipressin + albumin therapy if they failed to respond to albumin alone; 11 patients subsequently crossed over to receive terlipressin treatment.

Results:
Of a total of 46 randomized patients, fourteen (9 on terlipressin + albumin, 5 on albumin alone) completed 15 days of treatment; under "early termination," there were 5 deaths in terlipressin and 3 in the albumin-treated group. No patients were lost through the 90 day follow-up.

Mean age was 55-59 years (older population than OT-0401); 6-7 per group (26-30%) were $\geq$ 65 years; 13-16 per group (57-65%) were male; the population was 74% HRS type 1 and 26% HRS type 2; 100% had a history of cirrhosis, 61-82% due to alcohol; and 65% (15 per group) had precipitating events leading to HRS. Mean Child-Pugh score was 10.5-10.6 (median 10-11); mean MELD score about 28-29 (median 26-29); about 61-70% (14-16 patients per group) were classified as Child-Pugh score class C.

The mean baseline creatinine clearance was significantly higher in patients randomized to terlipressin + albumin vs. albumin alone (26.9 mL/min vs. 20.6 mL/min; p = 0.039).
Other statistically significant baseline imbalances included serum sodium (mean 124.5 terlipressin vs. 129 placebo, p=0.04) and body weight (terlipressin 76.2 kg vs. albumin 62.8 kg, p = 0.002).[11] There was a trend toward baseline higher central venous pressures in the terlipressin group (mean 12.4 terlipressin vs. 9.5 mm Hg in placebo, p= 0.08) implying that a component of the body weight was fluid; however, this is a "soft" finding in an open-label trial, and biases in measurements cannot be excluded.

In addition, 7 terlipressin vs. 1 albumin patients had a baseline total bilirubin > 30 mg/dL. It is not clear (although the possibility exists) that these differences impact or confound any result.

Efficacy analyses were based on the ITT population.

[11] Baseline body weights were higher in OT-0401, where the mean weight was 90.8 kg for terlipressin and 84.0 kg for placebo.

This study did not "win" on its primary efficacy endpoint. The survival curves show a favorable lean toward albumin alone.

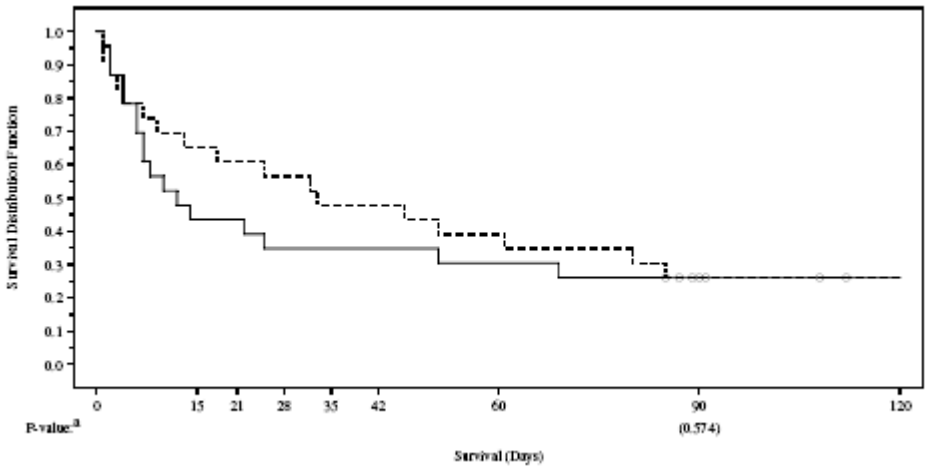

Figure 2. Kaplan-Meier plot of overall survival (ITT). Y-axis shows survival distribution function and x-axis shows survival (days). Dotted line = albumin alone; straight line = terlipressin + albumin.

No patients were lost during follow-up for survival. Six patients who received terlipressin + albumin (26.1%) and 7 patients who received albumin (7/23) were alive at Day 90 (source: TAHRS study report, table 4.1.5, page 72, ITT population and Figure 4.1.2, page 69). The median survival was 12.0 days for patients who received terlipressin + albumin and 33.0 days for patients who received albumin alone (source: medical-statistical review, page 45). Only one patient (albumin alone) underwent liver transplant during the 90-day study period; the analyses of transplant-free survival were consistent with overall survival results. Six patients in each group were counted as transplant-free survivors through Day 90.

The medical reviewer has stated that attention should be paid to the higher early mortality observed in patients on terlipressin + albumin vs. placebo, because of: 1. terlipressin's short half-life and activity; 2. potential dilution of a signal by Day 90 in this severely ill population; 3. confounding of Day 90 results by a significant proportion (48%) of placebo patients that subsequently received terlipressin "rescue" therapy.

The sponsor has argued that the survival curves are highly sensitive to imbalances in baseline prognostic factors because of the small patient population and that a much larger trial would be required for a statistically valid estimate of overall survival. The sponsor has identified 7 significant baseline prognostic factors (TAHRS CSR Section 4.2.5.2), of which 2 (serum sodium and total bilirubin) were imbalanced between treatment groups. The sponsor, adjusting for these differences, has claimed that the median overall survival increased from 12 to 25 days in the terlipressin + albumin group, and decreased from 33 to 14 days in the albumin group (p=NS).

However, the sponsor would need to show how they modeled and adjusted for baseline imbalances and whether they took into account potential adverse drug effects. In this small trial, one cannot know how baseline imbalances will affect results, including survival. Nonetheless, the burden is on the sponsor to show, with additional data, that terlipressin's

benefits outweigh any safety risk. This reviewer therefore agrees with the primary medical reviewer that attention should be paid to the early difference in survival and the sponsor should provide additional safety data in a future study.

7.1.3. Other efficacy studies:

The sponsor cited 17 prior literature studies, of which 9 were uncontrolled, open-label studies. Most involved smaller numbers of patients than OT-0401. There are few controlled, double-blind studies; one double-blind, placebo-controlled study (Hadengue) in the list did not state a primary endpoint. In short, the cited papers did not provide compelling support for the proposed claim.

7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

Dr. Xu, the primary medical reviewer, has expressed concern that the effect of terlipressin on SCr has not translated to any real clinical benefit. Furthermore, more treatment-emergent adverse events and slightly higher on-treatment mortality were observed in the terlipressin arm compared to control. Dr. Xu has concluded that terlipressin should not be approved; at least one additional adequate, well-controlled study should be conducted to demonstrate efficacy and safety for terlipressin in HRS type 1. This reviewer concurs.

Additional concerns of the medical and statistical reviewers included the following:

1. The primary endpoint was changed post-trial completion and the reviewers were not assured that the blinding was preserved.
2. Secondary endpoint analyses were different from the pre-specified analyses, with the new analyses open to confounding. As an example, the sponsor used SCr measurements obtained after dialysis and liver transplantation to demonstrate a change from baseline in SCr due to study medication.
3. Incomplete information was submitted to verify that subjects met diagnostic criteria for HRS type I.
4. Not all SCr values were submitted for review, including those obtained during the study but excluded from analysis.
5. Adverse events were found that were not included in the safety dataset; actual death dates were unknown or missing.

7.1.5. Pediatric use/PREA waivers/deferrals:

Since this IND has been granted orphan drug status, PREA is not applicable. From a literature search, childhood liver disease and hepatorenal syndrome appear to be rare (no incidence found) but can occur.[12]

[12] Debray D et. al. New Management Options for End-Stage Chronic Liver Disease and Acute Liver Failure. Pediatr Drugs 2006: 8(1): 1-13.

7.1.6. Discussion of notable efficacy issues *(resolved or outstanding).*

There have been ongoing discussions between the review team and the sponsor concerning the meaningfulness of the HRS reversal endpoint; effect of baseline imbalances on survival results; analysis of the change from baseline in creatinine; and missing creatinine data.

7.2. Safety

7.2.1. General safety considerations

A total of 90 HRS patients were exposed to terlipressin in the two clinical trials.[13] Out of this database only 4 patients received > 15 days of terlipressin; there is little experience regarding longer-term exposure. This safety database is small and will only exclude large safety signals. In addition, information concerning dose-related toxicity is extremely limited.

The sponsor also cites exposure in 300 patients given terlipressin in HRS published studies, and about 900 patients treated with terlipressin in clinical trials for esophageal variceal hemorrhage. While this information is helpful in terms of large signals and short-term exposure, the reviewers will not be in a position to evaluate the extent of exposure and safety monitoring.

7.2.2. Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

In study OT-0401, 6 terlipressin patients and 3 placebo patients died on treatment (all deaths occurred on or before study Day 5).[14] Five of the six terlipressin deaths were coded as due to "hepatic insufficiency" (3 out of the 5 had baseline SCr > 7.0). Seven of the on-treatment deaths (5 terlipressin, 2 placebo) occurred at three Russian sites, raising the issue of population, or regional variation, or some unknown other factor. Whether these deaths represent a sicker patient population who might not benefit from terlipressin, or whether there is an early mortality signal will need to be addressed with further safety data. In the Kaplan-Meier curves from TAHRS, the early survival showed a lean that was unfavorable for terlipressin.

In OT-0401, eight terlipressin and 2 placebo patients developed adverse events that led to dose reduction/interruption or withdrawal (medical-statistical review Table 21, page 33). Two terlipressin and no placebo patients (b) (6) and were noted to have "pulmonary hemorrhage" and "alveolar hemorrhage," respectively. A third terlipressin patient (b) (6) and one placebo patient (b) (6) were noted to have respiratory failure/pulmonary edema/hypoxic respiratory distress. For other adverse events potentially related to vasoconstrictor activity of terlipressin, there is one case of abdominal cramp and a case of finger/toe cyanosis, with no corresponding cases on placebo.

[13] The sponsor counts 93 in the safety population because 3 terlipressin patients were retreated.

[14] One should also note the Kaplan-Meier curve from TAHRS, which also was unfavorable for terlipressin early in therapy.

In the same study, bronchospasm and wheezing occurred in 6 (11%) terlipressin and 0 placebo patients. Gastrointestinal symptoms (abdominal pain and vomiting) also occurred more frequently in terlipressin patients vs. placebo.

In Table 25 of the medical-statistical review, there are 22 bleeding adverse events on terlipressin (39%) vs. 9 on placebo (16%); however, one patient could have had multiple bleeding events. From the electronic dataset AEDOSE.xpt., this reviewer counted 7 terlipressin patients and 3 placebo patients with bleeding events.[15]

In TAHRS, 3 terlipressin and 0 placebo patients developed dyspnea; 4 terlipressin and 1 placebo had pulmonary edema; 5 terlipressin and 1 placebo patient developed abdominal pain, 3 terlipressin and 0 placebo patients developed intestinal ischemia. While the numbers are small, the increased occurrence on terlipressin is consistent with results from OT-0401.

In summary, in a small safety database, respiratory and GI adverse events (including abdominal pain and intestinal ischemia) were seen with terlipressin use. There also was a slight numerical increase in patients treated with terlipressin who had bleeding events; it is not clear whether this increase constitutes a "signal" vs. "play of chance" in a sick population; a bleeding signal would be ironic considering terlipressin use in esophageal variceal hemorrhage. There is also an imbalance (unfavorable for terlipressin) in on-treatment mortality in OT-0401 and early mortality in TAHRS that should be addressed with additional safety data.

7.2.3. Safety update

No new clinical trial information was submitted in the safety update.

7.2.4. Immunogenicity

A review of product immunogenicity was performed by the Division of Therapeutic Proteins. The review analyzed the validation report for a screening assay to assess development of antibodies; and the results for screening of 246 patients from the Phase III study. The sponsor concluded that no significant antibody had been detected in patient samples.

According to the reviewers, the information on the screening assay to assess immune responses to the product is incomplete and internally inconsistent hindering the interpretation of the submitted data. There are issues regarding sensitivity and specificity of the assay; absence of raw data; and the concern that the binding of the sponsor's standard antibody may not reflect binding of human antibodies to the product. In their review, the Division made several recommendations which have been sent to the sponsor; the Agency is currently awaiting the sponsor's response.

7.2.5. Discussion of primary reviewer's comments and conclusions

[15] Anemia was not considered a bleeding event and excluded from these counts.

The primary medical reviewer was concerned about an observed higher mortality rate in the terlipressin arm in TAHRS and higher on-treatment deaths in OT-0401. The sponsor attributed on-treatment deaths in OT-0401 to baseline imbalances and a sicker population. This reviewer feels that the issue of on-treatment deaths will be difficult to resolve without further safety data.

7.2.6. Pre-Approval Safety Conference (If an NME that will be approved)
Not applicable.

8. Advisory Committee Meeting

Following discussion with the review team, division director and office director, as well as a teleconference with the sponsor, it was decided not to take this application to an advisory committee at this time.

9. Other Relevant Regulatory Issues

None at this time.
Examples might include Application Integrity Policy (AIP), exclusivity or patent issues of concern, or other regulatory matters.

10. Financial Disclosure

There are no known financial disclosure issues.

11. Labeling

As the clinical-statistical team is not recommending approval, no clinical labeling recommendations will be made at this time.

11.1. Proprietary name
The sponsor's proposed product name is Lucassin. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name conditionally acceptable for this product.

11.2. Physician labeling
The following labeling modifications were recommended by the pharmacology/toxicology reviewer and clinical pharmacology reviewer, respectively:

(b) (4)

(b) (4)

(b) (4)

11.3 Carton and immediate container labels: Not reviewed.
11.4 Patient labeling/Medication guide: Not applicable.

12. DSI Audits

In addition to the contract research organization (b) (4), four sites (b) (4) from study OT-0401 were inspected. These sites were chosen due to enrollment or concerns about documentation.

The final report of DSI audits is pending at the time of this review. If needed, an addendum to this review may be filed when appropriate.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

Based on this application, terlipressin should not be approved for the treatment of hepatorenal syndrome, type 1. A complete response letter should be issued to the sponsor, including deficiencies and recommendations from the various disciplines.

13.2. Comments to be conveyed to the applicant in the regulatory action letter:

CMC:

(b) (4)

2. The specification for drug substance should include testing for heavy metals to ensure that every batch meets the USP <231> requirement. Please provide revised drug substance specification.

3. The analytical method intended for quantitation of residual solvents in the drug substance is considered inferior to USP method based on LOD and LOQ values in the validation report. Additionally, data provided in attachment 2 in response to the information request letter (dated 06-AUG-09) are inconsistent with the LOD and LOQ values per validated method. For example, LOD for DMF is (b) (4) ppm per validation data whereas the results reported in attachment 2 were (b) (4) ppm. Provide an explanation.

4. Based on the results provided for three drug substance lots (S.3.2.2.3 Table 14), we recommend that you incorporate testing for (b) (4) (b) (4) in the specification for drug substance.

Clinical Pharmacology:

1. Exposure-response relationships were not adequately explored in study OT-0401, and should be evaluated in future studies. Collecting pharmacokinetic data on study day1 in all subjects will facilitate a more informative and robust terlipressin exposure-response analysis.

2. In study OT-0401, patients were treated for variable number of days after SCr had reached values < 1.5 mg/dL, confounding the interpretation of the observed change in SCr. In future studies patients should be continued on the assigned treatment till the end of study.

3. More number of subjects with baseline SCr > 7 mg/dL were randomized to the terlipressin treated group in study OT-0401, resulting in a baseline imbalance. In future studies, modify the inclusion criteria to include an upper limit for SCr so as to achieve similar baseline SCr in all treatment arms.

Clinical:

1. You have submitted two studies, OT-0401 and TAHRS, to support efficacy and safety in the treatment of hepatorenal syndrome. Neither study met its prespecified primary endpoint. Study OT-0401 demonstrated a transient reduction in SCr in patients randomized to terlipressin without evidence of a sustained improvement in renal function. There was no demonstrated improvement in survival, likelihood of liver transplant or prevention of dialysis in patients receiving terlipressin. Furthermore, in both studies, patients treated with terlipressin experienced more treatment-emergent adverse events. Therefore, there is insufficient evidence of benefit based on available data.

   We recommend that you conduct at least one additional study to support a benefit and provide further safety characterization. If you conduct one additional study, the endpoint should be robust and meaningful. Please see specific recommendations in our meeting minutes (9/3/09) under "additional actions to support approval of terlipressin in the treatment of HRS type 1."

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARI L TARGUM
10/07/2009

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	22-231
Submission Type; Code:	Original, N_000
Applicant Name:	Orphan Therapeutics
Submission Dates:	May 27, 2008
Brand Name:	Lucassin ®
Generic Name	Terlipressin
Dosage Form:	Lyophilized powder for IV injection
Dosage Strengths:	1 mg terlipressin/vial
Proposed Indication:	Hepatorenal syndrome type 1
OCP Division:	Division of Clinical Pharmacology 1
Primary Reviewer:	Divya Menon-Andersen
Pharmacometrics secondary reviewer/Team leader:	Pravin Jadhav
Clinical pharmacology secondary reviewer/Team Leader:	Rajnikanth Madabushi

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1 EXECUTIVE SUMMARY

Orphan Therapeutics is seeking approval of terlipressin (Lucassin®) for use in the treatment of hepatorenal syndrome (HRS) type1. HRS is a rare and fatal condition that occurs in patients with end stage liver disease, where changes in the splanchnic circulation caused by the liver disease result in poor blood flow to the kidney and subsequent deterioration of renal function. Currently, there are no FDA approved drugs for the treatment of HRS. Hence, terlipressin was granted orphan status in October 2004 and fast track designation in April 2005 (rolling NDA and subsequent priority review status).

Terlipressin is a 12 amino acid containing synthetic peptide analogue of vasopressin. It is formulated as a lyophilized powder, to be reconstituted for intravenous administration as a slow bolus injection. The sponsor proposes a starting dose of (b) (4) mg/kg to be administered every six hours. The dose may be doubled to (b) (4) mg/kg after (b) (4) days, if serum creatinine (SCr) does not decrease by 30% from baseline. Treatment with terlipressin is to be discontinued (b) (4) days after SCr ≤ 1.5 mg/dL has been achieved; (b) (4) (b) (4) Treatment with terlipressin should not be continued beyond 14 days.

The application contains a single pivotal clinical study, Study OT-0401 (pharmacokinetics and effectiveness) conducted in patients with HRS type 1, a supportive open label safety study in patients with HRS type1/2, and *in vitro* studies evaluating the potential for terlipressin to inhibit or induce CYP enzymes.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP1) reviewed NDA 22-231. The NDA is acceptable from a clinical pharmacology perspective, provided that a satisfactory agreement is reached between the sponsor and the Agency regarding language in the package insert.

Comments

1. From the limited pharmacokinetic (PK) data submitted in this application, it appears that the pharmacokinetics of terlipressin in HRS type 1 patients are similar to those previously reported in healthy subjects. The primary mechanism for clearance of terlipressin is via degradation by tissue peptidases in almost all organs. Since, tissue peptidases in HRS type 1 patients are not expected to be very different from those in healthy subjects (except the liver), this is acceptable. However, the sparse sampling strategy designed based on previously reported data from healthy subjects was not carried through as planned, leading to poor characterization of terlipressin PK in HRS type 1 patients.

Recommendations for future studies

1. Exposure-response relationships were not adequately explored in study OT-0401, and should be evaluated in future studies. Collecting pharmacokinetic data on study day1 in all subjects will facilitate a more informative and robust terlipressin exposure-response analysis.
2. In study OT-0401, patients were treated for variable number of days after SCr had reached values < 1.5 mg/dL, confounding the interpretation of the observed

change in SCr. In future studies patients should be continued on the assigned treatment till the end of study.

3. More number of subjects with baseline SCr > 7 mg/dL were randomized to the terlipressin treated group in study OT-0401, resulting in a baseline imbalance. In future studies, modify the inclusion criteria to include an upper limit for SCr so as to achieve similar baseline SCr in all treatment arms.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Orphan Therapeutics conducted a single clinical study (OT-0401) to support approval of terlipressin. The sponsor also acquired the rights to an open-label study (TAHRS) conducted in patients with HRS type1/2, and submitted it to the NDA as a supportive study. Terlipressin exposure was not assessed in TAHRS.

The key clinical pharmacology findings are:

- The PK of terlipressin in HRS type 1 patients were characterized by population pharmacokinetic (PPK) analysis. The estimated clearance was 32.3 L/h and the volume of distribution in central compartment was 37 L. The terminal elimination half-life is ~ 1 hr.
- The PK of terlipressin in HRS type 1 patients appear to be similar to that observed in healthy subjects. Terlipressin is degraded by tissue petidases and this is not expected to be different between healthy and HRS patients.
- A relationship between terlipressin exposure and change in serum creatinine was not apparent from the data collected in study OT-0401.
- None of the patients treated with terlipressin developed antibodies to the product.

2 QUESTION BASED REVIEW

This is an abridged version of the QBR.

2.1 General Attributes of the Drug

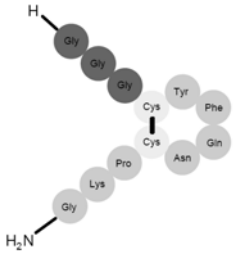
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Chemical name: (2S)-1-[(4S,7S,10S,13S,16S,19S)-19-[[2-[[2-[(2-Aminoacetyl)amino]acetyl]amino]acetyl]amino]-13-benzyl-10-(2-carbamoylethyl)-7-(carbamoylmethyl)-16-[(4-hydroxyphenyl)methyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicosane-4-carbonyl]-N-[(1S)-5-amino-1-(carbamoylmethylcarbamoyl)pentyl]pyrrolidine-2-carboxamide

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

Molecular weight: 1227.4

Structural formula:



Solubility: Freely soluble in aqueous solutions in the pH range of (b) (4)

Formulation: Sterile, lyophilized powder in a clear glass vial containing 1mg of terlipressin diacetate pentahydrate to be reconstituted with 5 mL of 0.9% sterile NaCl prior to administration.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Terlipressin, a vasopressin analogue, is a systemic vasoconstrictor selective to vasopressin V1 vascular receptors. In HRS type 1 patients (who have a dilated splanchnic circulation), the V1 receptor mediated vasoconstrictor activity of terlipressin is hypothesized to cause an increase in effective arterial volume, an increase in mean arterial pressure, and normalization of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system) resulting in increased renal perfusion and renal function.

Terlipressin is indicated in the treatment of HRS type 1.

2.1.3 What are the proposed dosages and routes of administration?

Terlipressin is formulated for intravenous administration as a slow bolus (~ 2 min) injection.

A starting dose of 1mg/kg, to be administered every six hours is proposed for the treatment of HRS type 1. The dose may be doubled to (b) (4) mg/kg after three days, if serum creatinine does not decrease by 30% from the baseline value. Treatment with terlipressin is to be discontinued if either of the following occurs: (1) (b) (4) days after SCr ≤ 1.5 mg/dL is achieved (2) (b) (4) (3) the patient (b) (4) (4) after 14 days of administration.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

A single clinical study was conducted with terlipressin to support dosing. The clinical pharmacology sections of study OT-0401 were reviewed (pharmacometrics review), and is presented in Appendix 4.2.

Table 1: key design features of studies conducted with terlipressin.

Study number	Design	Study population	Treatments	Endpoint
OT-0401 Pivotal	Double-blind, placebo controlled, randomized study	HRS type 1 n=112	Terlipressin (1 mg q6h, 2 mg q6h), matching placebo	PK, Exposure-response, Conc-QT, Immunogenicity, Efficacy, Safety
TAHRS Supportive	Open label, albumin controlled, randomized study	HRS type 1 / type 2 n=46	Terlipressin (1 mg q4h, 2 mg q4h) + albumin, albumin	Efficacy, Safety

In addition, the sponsor also submitted *in vitro* metabolism studies evaluating the potential for CYP inhibition or induction, and a red blood cell fragility study. All in vitro studies were reviewed and the individual study reports are presented in Appendix 4.2.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Treatment success on day 14, defined as percentage of patients alive with HRS reversal as determined by two consecutive SCr measurements < 1.5 mg/dL within 48 h, was the protocol defined primary endpoint in the pivotal study OT-0401. Subsequently, after database closure and before unblinding, the sponsor changed the primary endpoint to HRS reversal as determined by a single SCr measurement < 1.5 mg/dL.

Terlipressin is a systemic vasoconstrictor that is hypothesized to improve renal perfusion and function; therefore an endpoint based on decrease in SCr is an appropriate measure of its efficacy.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Terlipressin was measured using a validated HPLC/MS/MS method. Please refer to section 2.6 for details of the bioanalytical method. Lysine-terlipressin, the active metabolite of terlipressin was only monitored.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Terlipresssin exposure-response relationships for treatment success and change from baseline SCr were explored graphically. No relationships between terlipressin exposure and treatment success or change from baseline SCr were apparent.

Note that the exposure-response data available from study OT-0401 were limited in order to conduct informative analyses. Of the 56 patients randomized to the terlipressin treated group, 22 patients discontinued from the study before day 3. All pharmacokinetic measurements in OT-0401 were made after study day 3; hence, terlipressin exposure data were not collected in a significant portion of the patients in the study.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

Terlipresssin exposure-response relationships for adverse events (death, all SAE, organ failure, TIPS, TRT related SAE) were explored graphically. No relationships between terlipressin exposure and any adverse event were apparent.

2.2.4.3 Does this drug prolong QT/QTc Interval?

The effect of terlipressin on the QT interval could not be determined because of the limitations of the study. Please refer to the review by CDER DCRP QT Interdisciplinary review team (DARRTS, review date: September 4, 2008).

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single and multiple dose PK parameters?

Single Dose Study:

Single dose pharmacokinetics of terlipressin were not evaluated in this NDA. According to a previously reported study in healthy subjects, terlipressin clearance was estimated to be 41.5 L/h, following administration of a single IV dose. The mean elimination half-life was reported to be about 1 h.

Multiple dose PK

The pharmacokinetics of terlipressin following multiple dosing (1 mg/kg, 2 mg/kg) were characterized by population pharmacokinetic analysis in study OT-0401. A clearance of 32.2 L/h was estimated in a typical HRS patient, with an inter-subject variability of 68%. The mean terlipressin half-life was estimated to be about 1 h.

2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

The pharmacokinetics of terlipressin in patients with HRS type 1 appear to be similar to that observed in healthy subjects.

Plasma terlipressin concentration data were collected in study OT-0401 following a sparse sampling scheme. A comparison of the observed terlipressin plasma concentrations in study OT-0401, with historical data collected in healthy subjects[1] is presented in **Figure 1**.

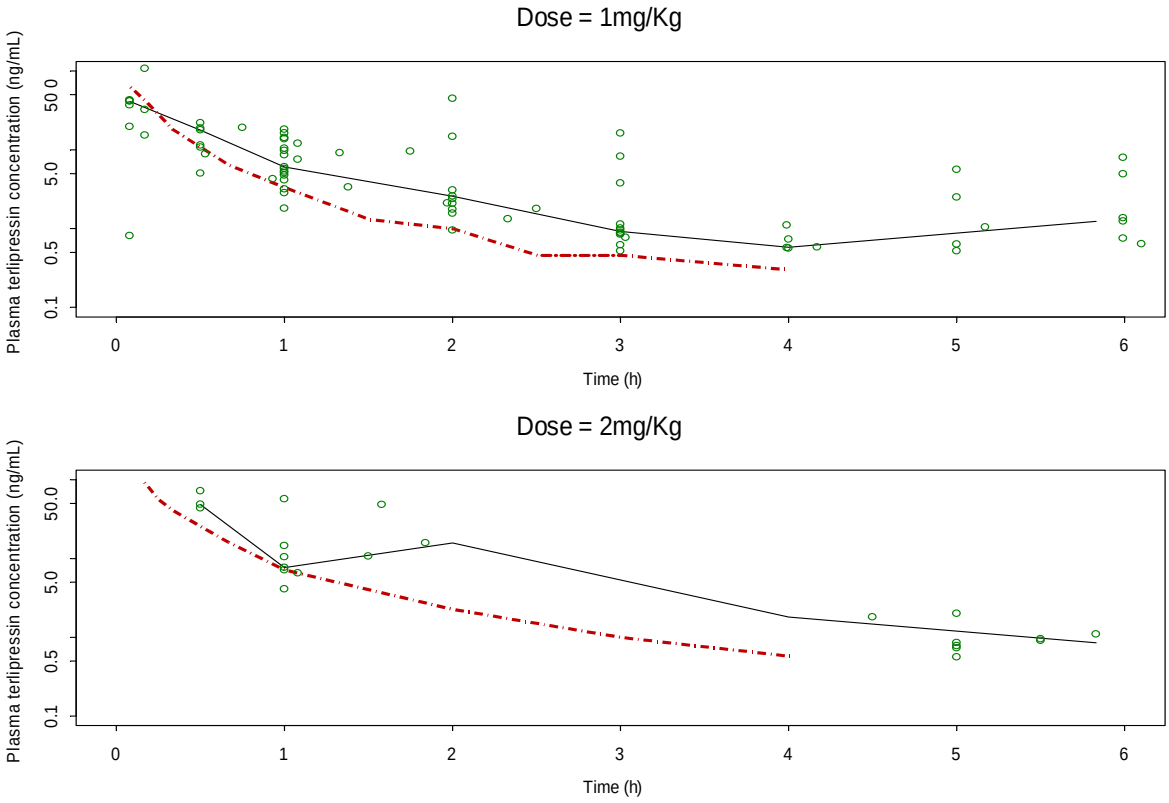


Figure 1: Plot of observed terlipressin plasma concentration (open circles) versus time in HRS type 1 patients, in comparison with mean terlipressin plasma concentrations reported in healthy subjects (broken line). The solid line represents the median concentrations observed in HRS type 1 patients.

As seen in **Figure 1**, the observed concentrations in patients with HRS type 1 are comparable to that reported in healthy subjects, who received equivalent doses. Results of the PPK analysis indicate similar clearance of terlipressin in HRS type 1 patients and that

[1] Plasma terlipressin concentration data in healthy subjects were obtained from the study by *Nilsson et al., Drugs Exptl Clin Res XVI (6) 370*. Plasma samples were collected for up to 4 h following administration of a single IV dose of 10 (n=14) or 20 (n=8) µg/kg of terlipressin in healthy subjects.

reported in healthy subjects (32.3 L/h in a typical HRS type 1 patient vs. 41.5 L/h in a healthy subject[2]).

It should be noted that the PK information in HRS patients is very limited, and that some of the model parameters in the PPK analysis (V2 - volume of distribution of the peripheral compartment, and Q - inter-compartmental CL) were fixed to that estimated in healthy subjects.

2.2.5.3 What are the characteristics of drug metabolism?

According to *in vitro* studies reported in the literature, terlipressin is degraded by several tissue peptidases in almost all organs. A greater degradation activity is reported in the liver and kidneys[3].

The active metabolite, lys-vasopressin, is formed by the stepwise cleavage of the terminal glycyl residues of terlipressin. Lys-vasopressin undergoes rapid degradation via C-, N-terminus, and disulfide bond cleavage.

2.2.5.4 What are the characteristics of drug elimination?

Based on data reported in healthy subjects, < 1% of terlipressin and < 0.1% of lys-vasopressin is eliminated in urine. The elimination half-life of terlipressin and its active metabolite lys-vasopressin is about 1 h and 6 min, respectively.

2.2.5.5 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Based on data reported in healthy subjects, plasma concentrations increase proportionately with dose.

2.2.5.6 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

Based on the PPK analysis of the data collected in HRS type 1 patients, the inter-subject variability in clearance and volume of distribution is 68 and 98%, respectively.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on PPK analysis of the data collected in study OT-0401, no significant effect of weight, gender, age, creatinine clearance, Child-Pugh Score, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin were observed on terlipressin exposure.

---

[2] Results of NCA

[3] *Plate 1995*, Studies on the localization and kinetics in the degradation of the synthetic vasopressin slow-release preparation, dissertation toward the degree of Doctor of Medicine.

2.4 Extrinsic Factors

2.4.1 What are the drug-drug interactions?

2.4.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Terlipressin is degraded by tissue peptidases in almost all organs. It does not inhibit or induce CYP enzymes. **Hence, no *in vivo* drug-drug interactions are anticipated.**

2.4.1.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No, terlipressin does not inhibit or induce CYP enzymes.

The potential for inhibition or induction of CYP enzymes was evaluated *in vitro* in studies 302-1173 and 302-1172, respectively.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Terlipressin is formulated for intravenous administration.

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?

Terlipressin concentrations in plasma were measured using a validated HPLC/MS/MS method. Details of the bioanalytical methods used to support pharmacokinetics in study OT-0401 are provided in **Table 2**. The method satisfied all criteria for 'method validation' and 'application to routine analyses' set by the Bioanalytical Guidance, and was therefore acceptable.

Table 2: Assay validation results for terlipressin and lys-vasopressin (Ref: Method validation report, study AA20116-01, vol 3)

	Terlispressin	**Lys-vasopressin**
Standard curve	0.5 to 50 ng/mL (weighted $1/x^2$, r=0.9963)	0.1 to 10 ng/mL (weighted $1/x^2$, r=0.9942)
Precision (%CV)	QC samples (0.3, 3.0, 7.5 ng/mL) Within run→ 1.0 to 4.6 % Between run→3.7 to 4.4 % At LLOQ (0.1 ng/mL): Within run→3.7 to 7.7 % Between run→6.4 %	No acceptance criteria applied
Accuracy (Bias)	QC samples (0.3, 3.0, 7.5 ng/mL) Within run→ -5.3 to 6.7 % Between run→-0.5 to 0.7 % At LLOQ (0.1 ng/mL): Within run→-4.6 to 5.0 % Between run→0.2 %	No acceptance criteria applied

Internal standard	d_{11}-terlipressin source: (b) (4)	
Reference standard	Terlipressin acetate Source: Multiple peptide systems, Lot no. 2K04002, purity: 99.1%	Lys-vasoppressin trifluoroacetate Source: (b) (4) (b) (4) purity: >99%
Specificity	No interference	
Recovery	d_{11}-terlipressin: 44% terlipressin: not determined	Not determined
Matrix	EDTA human plasma	EDTA human plasma
Stability	Post prep: 97 h at 5°C Long term: 210 days at -20°C Short term: 13 h at RT Freeze-thaw: 5 cycles	

2.6.2 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

An indirect ELISA was used to detect the presence of anti-drug antibodies in plasma. Details of the assay are presented in **Table 3**. Please refer to Dr. Michael Phelan's review for further details. (e-mail communication: August 3, 2009)

Table 3: Validation parameters for immunoassay detecting antibodies to terlipressin (Ref: Dr. Michael Phelan's review, e-mail communication: August 3, 2009)

Assay type	Indirect ELISA
Controls	Normal human plasma was spiked with rabbit anti-arginine vasopressin polyclonal serum such that, after dilution of 1:100 in blocking buffer, three control samples are generated containing 250, 50 or 5 ng/ml. Each of these appear to be tested in duplicate on each ELISA plate.
Standards	Rabbit anti-arginine vasopressin in two-fold dilution series from 500 to 3.9 ng/ml in blocking buffer.
Cut-off	3 ng/ml after 1;100 dilution of the patient sample in blocking buffer. This cut-off arithmetically rises to 300 ng/ml in undiluted plasma and, sometimes, is reported thus.
Recovery	One normal human sera and the blocking buffer control were spiked with rabbit anti-arginine vasopressin polyclonal serum to yield three final concentrations of each sample and buffer (200, 50 and 5 ng/ml). Recoveries of the spike over the background, determined in quintuplicate, ranged in mean from 80% to 113% for buffer and serum.
Sensitivity	Note "Cut-Off" comments. The sensitivity was determined from three independent assays of 10 samplings, tested in duplicate, of human pooled plasma diluted 1:100 in blocking buffer. The values of each experimental point were interpolated from the standard curves and all the values meaned. The mean (1.131 ng/ml) and standard deviation around the mean (0.603 ng/ml) were used to arrive at the assay sensitivity (mean plus 3 x SD = 2.941, rounded to 3.0 ng/ml).
Dilutability	(If I understand what this term means) The sponsor has provided evidence of linearity, with text and graphics, using a starting material of 250 ng/ml of rabbit

	antiserum serially diluted over the dilution range 1:2 to 1:64 with either blocking buffer or normal human plasma. According to the sponsor, the linearities were comparable with mean linearities ranging from 103% to 117 %.
Accuracy	Accuracy of the assay was determined by replicate analyses of three concentrations (250, 50 and 5 ng/ml) of anti-vasopressin Ab standard spiked in human plasma with five determinations per concentration level. Mean values generated by the five points in each concentration were determined along with SD and % CV. Mean assay accuracy, according to the sponsor ranged from 80 % to 92 %.
Precision	Studies using replicates of QC controls of plasma spiked with anti-vasopressin Ab (5, 50 or 250 ng/ml) ranged from 11.3 % to 16.8 % for intra-assay variability and 16-22% for inter-assay variability.
Specificity	The rabbit anti-arginine vasopressin serum binds to Terlipressin (detection limit 1:25, 600 and maximum absorbance, 1.9 to 2.0) but also to arginine vasopressin (detection limit 1:25,600 and maximum absorbance, 0.7) and lysine vasopressin (detection limit 1:3,200 and maximum absorbance, 0.3)
Interference	No specific materials provided to support interference
Robustness	No specific materials provided to support robustness
Stability	The rabbit antibodies, especially at the higher concentration, in the presence of human plasma, have been shown to be relatively stable for 3 freeze-thaw cycles. No significant (rather, increases) in recovery from spiked samples was evident when stored at room temperature or at 4ºC for up to 24 hours. In addition, frozen samples (-20 ºC) demonstrated good recovery,(96 % to 118 %) after three months.

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for XXXXXX and finds it acceptable pending the following revisions shown below. ~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added.

Pharmacokinetics

(b) (4)

4 APPENDICES

4.1 Proposed Package Insert (Annotated)

The complete package insert can be found at

(b) (4)

4.2 Individual Study Reviews

4.2.1 Study 302-1173 (CYP 450 Inhibition)

Determination of the Inhibitory potential of Terlipresin Pentahydrate on the Activities of CYP1A2, CYP1A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in human liver microsomes.

Protocol number: 1173

4.2.1.1 Objective

To determine the potential of terlipressin to inhibit CYP 450 enzymes, using specific CYP 450 substrates in human liver microsomes.

4.2.1.2 Study Design

Human liver microsomes pooled from a minimum of ten human donors, were incubated with terlipressin (final concentration 10, 50, 500, 5000 ng/mL) and a CYP 450 enzyme specific substrate at 37±1°C (**Table 1**).

Table 1: CYP 450 enzymes specific substrates used in the study (Ref: Study report, vol 1)

CYP 450 enzyme	Enzyme specific substrate	Sustrate Conc.
CYP 1A2	Phenacetin	50 µM
CYP 2A6	Coumarin	8 µM
CYP 2B6	S- mephenytoin	1 mM
CYP 2C8	Paclitaxel	5 µM
CYP 2C9	Tolbutamide	150 µM
CYP 2C19	S- mephenytoin	50 µM
CYP 2D6	Dextromethorphan	5 µM
CYP 2E1	Chlorzoxazone	50 µM
CYP 3A4	Testosterone	100 µM

At the end of the incubation period, the reaction was terminated by addition of acetonitrile or methanol. Vehicle control and ketoconazole (1 µM) positive control treatment groups were also included in the study. The specific metabolites were assayed using a HPLC-UV or HPLC/MS/MS method.

Reviewer's comment:

The CYP 450 enzymes evaluated, and the enzyme specific substrates used in this study follow the 'Guidance for Industry:DDI , and are acceptable.

4.2.1.3 Data analysis

Enzyme activity (mean ± SD) was estimated and results expressed as percent vehicle control.

4.2.1.4 Results

CYP 3A4 acitivity was reduced by > 80% when the test system was incubated with 1 µM ketoconazole. No significant inhibition of CYP 450 enzyme activity was observed at any of the terlipressin concentrations tested.

4.2.1.5 Conclusion

Terlipressin does not inhibit CYP 450 enzymes at concentrations upto 5000 ng/mL. Since therapeutic concentrations are not expected to exceed 100 ng/mL, the results of the study suggest that the potential for causing CYP 450 mediated pharmacokinetics drug interactions is low.

4.2.2 Study 302-1172 (CYP 450 Induction)

Evaluation of the induction potential of terlipressin pentahydrate diacetate on the activities of CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4 in human hepatocytes.

Protocol number: 1172

4.2.2.1 Objective

To determine the potential of terlipressin to induce CYP 450 enzymes, using specific CYP 450 substrates in human hepatocyte cultures.

4.2.2.2 Study design

Human hepatocytes (obtained from three human donors) were incubated with terlipressin (final concentrations - 50, 500, 5000 ng/mL) for 48 ±3 h, following which CYP 450 enzyme specific substrates were added. The metabolites were measured using HPLC-UV or HPLC/MS/MS methods. The CYP 450 enzyme specific substrates and substrate concentrations used in the study are presented in **Table 1**.

Table 1: CYP 450 enzyme specific substrates and substrate concentrations used in the study. (Ref: Study report, vol 1)

CYP 450 enzyme	Enzyme specific substrate	Sustrate Conc.
CYP 1A2	Phenacetin	100 µM
CYP 2A6	Coumarin	100 µM
CYP 2B6	S- mephenytoin	1 mM
CYP 2C9	Tolbutamide	50 µM
CYP 2C19	S- mephenytoin	100 µM
CYP 2D6	Dextromethorphan	16 µM
CYP 2E1	Chlorzoxazone	300 µM
CYP 3A4	Testosterone	125 µM

Hepatocytes incubated with the vehicle, and omeprazole (50 µM, CYP 1A2) and rifampin (25 µM, CYP 3A4) were used as negative and positive controls for the test system, respectively.

Reviewer's comment:

The CYP 450 enzymes specific substrates used in this study follow the 'Guidance for Industry:DDI , and are acceptable.

4.2.2.3 Results

CYP 1A2 acitivity was increased by > ten fold when the test system was incubated with 50 µM omeprazole. A five fold increase in CYP 3A4 enzyme activity was observed when the test system was incubated with 25 µM rifampin. No significant increase in CYP 450 enzyme activity was observed at any of the terlipressin concentrations tested.

4.2.2.4 Conclusion

Terlipressin does not induce CYP 450 enzymes at concentrations upto 5000 ng/mL, suggesting that the potential for causing CYP 450 mediated pharmacokinetics drug interactions is low.

4.2.3 Study CB04-5046-EV-PA (Red blood cell fragility)

Effect of terlipressin on human red cell fragility *in vitro*.

Protocol number: CB04-5046-EV-PA

4.2.3.1 Objective

To assess the effect of terlipressin on human red blood cell fragility.

4.2.3.2 Study design

Terlipressin was incubated with human blood samples for 30 minutes according to the schematic presented in **Table 1**, following which the samples were centrifuged and hemoglobin concentration in the supernatant was determined.

Table 1: A schematic of the study design.

Treatment	**Incubation**	**Terlipressin concentration (ng/mL)**
None	Room temperature	0
Saline	37 °C	0
Terlipressin	37 °C	17
Terlipressin	37 °C	57
Terlipressin	37 °C	170

Reviewer's comment: The study design is acceptable because appropriate concentrations were evaluated at 37℃.

4.2.3.3 Data analysis

The results were analyzed using ANOVA.

4.2.3.4 Results

Hemoglobin concentration in the supernatant following incubation with terlipressin is presented in **Table 2**.

Table 2: Hemoglobin concentration in the supernatant following incubation with terlipressin and saline. (Ref: Study report, vol 1)

Subject	RT Control			37° Control			17 ng/ml			57 ng/ml			170 ng/ml		
	Rep 1	Rep 2	Avg	Rep 1	Rep 2	Avg	Rep 1	Rep 2	Avg	Rep 1	Rep 2	Avg	Rep 1	Rep 2	Avg
1M	15.8	15.8	15.8	19.4	19.5	19.5	23.4	23.4	23.4	19.7	19.6	19.7	23.4	23.4	23.4
2M	12.3	12.2	12.3	13.3	13.3	13.3	14.2	14.2	14.2	12.8	12.7	12.8	11.2	11.2	11.2
3M	11.0	11.0	11.0	11.0	11.0	11.0	10.7	10.7	10.7	10.5	10.5	10.5	10.6	10.6	10.6
4M	5.6	5.6	5.6	5.8	5.8	5.8	5.2	5.2	5.2	4.8	4.8	4.8	6.2	6.2	6.2
5M	7.3	6.2	6.8	7.6	11.3	9.5	11.4	11.0	11.2	9.7	8.3	9.0	10.9	11.4	11.2
Mean			10.3			11.8			12.9			11.3			12.5
Std Dev			4.2			5.1			6.7			5.5			6.4
1F	6.0	5.9	6.0	7.4	7.4	7.4	8.0	8.0	8.0	8.2	8.2	8.2	6.0	6.0	6.0
2F	8.2	8.2	8.2	9.7	9.7	9.7	10.8	10.8	10.8	8.0	8.0	8.0	7.8	7.8	7.8
3F	5.1	5.3	5.2	6.1	6.2	6.2	5.5	5.5	5.5	5.4	5.4	5.4	6.2	6.2	6.2
4F	7.2	7.2	7.2	8.1	8.1	8.1	6.7	6.7	6.7	7.5	7.5	7.5	7.5	7.5	7.5
5F	4.7	4.0	4.4	4.1	4.9	4.5	4.4	4.4	4.4	5.4	4.5	5.0	3.5	4.7	4.1
Mean			6.2			7.2			7.1			6.8			6.3
Std Dev			1.5			2.0			2.5			1.5			1.5

As seen in **Table 2**, there is no significant difference in supernatant hemoglobin concentrations between the terlipressin treated groups and the control group at 37 °C.

4.2.3.5 Conclusion

Terlipressin when used in concentrations upto 170 ng/mL dose not appear to cause any significant hemolysis.

4.3 Pharmacometrics Review

Summary of findings

The purpose of this review is to address the following key questions.

Key review questions

1. **Are the pharmacokinetics of terlipressin in subjects with hepatorenal (HRS) type 1 similar to that in healthy subjects?**

The pharmacokinetics of terlipressin in patients with HRS type 1 are similar to that observed in healthy subjects. Plasma terlipressin concentration data were collected in study OT-0401 following a sparse sampling scheme. A comparison of the observed terlipressin plasma concentrations in study OT-0401, with historical data collected in healthy subjects[4] is presented in **Figure 1**.

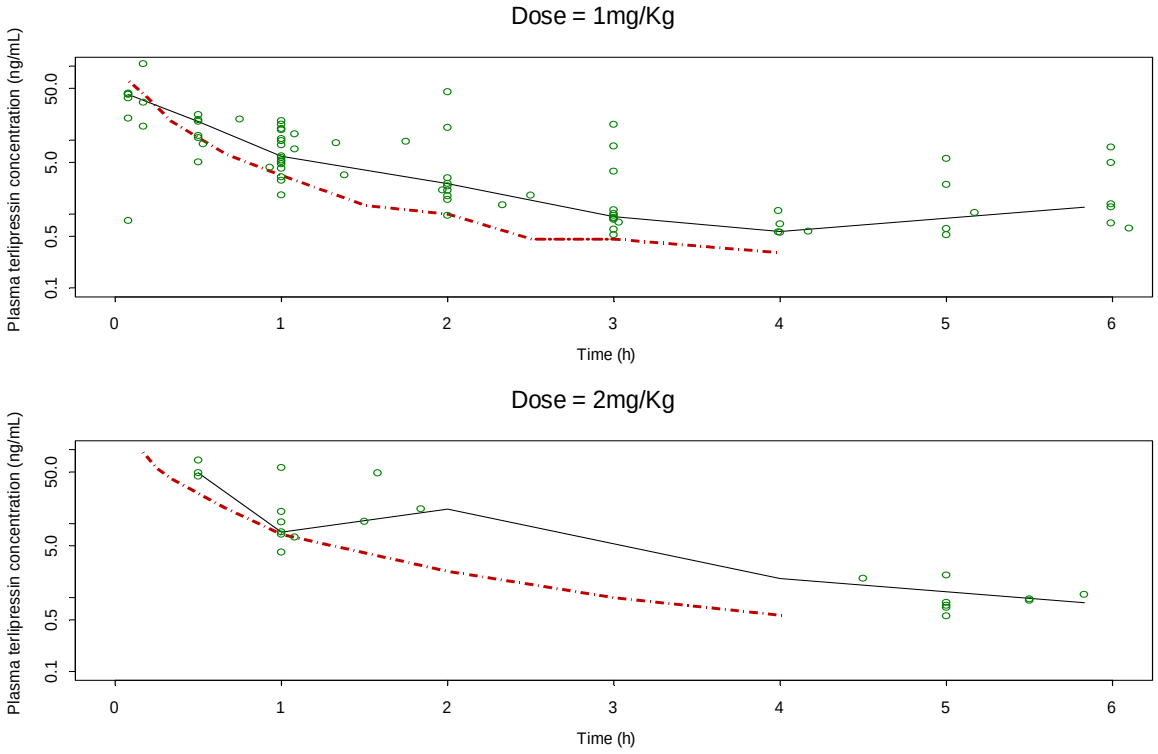


Figure 1: Plot of observed terlipressin plasma concentration (open circles) versus time in HRS type 1 patients, in comparison with mean terlipressin plasma concentrations reported in healthy subjects (broken line). The solid line represents the observed median concentrations in HRS type 1 patients.

As seen in **Figure 1**, the observed concentrations in patients with HRS type 1 are comparable to that reported in healthy subjects, who received equivalent doses. Results of the PPK analysis indicate similar clearance of terlipressin in HRS type 1 patients and that

[4] Plasma terlipressin concentration data in healthy subjects were obtained from the study by *Nilsson et al., Drugs Exptl Clin Res XVI (6) 370*. Plasma samples were collected for up to 4 h following administration of a single IV dose of 10 µg/kg (n=14) or 20 (n=8) µg/kg of terlipressin in healthy subjects. HRS patients in OT-0401 received 12 or 24 µg/kg.

reported in healthy subjects (32.3 L/h in a typical HRS type 1 patient vs. 41.5 L/h in a healthy subject[5]).

2. Does the current dataset provide evidence of an effect of terlipressin on serum creatinine?

Serum creatinine (SCr) data collected in study OT-0401 suggest an effect of terlipressin on SCr in patients with HRS type 1 (**Figure 2**). A larger number of patients in the terlipressin treated group exhibit a decrease in SCr from baseline, compared to patients in the placebo group. An arbitrary SCr value of 1.5 mg/dL was selected as a threshold value for defining HRS reversal in study OT-0401. While 15 individuals in the terlipressin treated group had SCr values < 1.5 mg/dL by study day 7, only six individuals in the placebo treated group had SCr values < 1.5 mg/dL, indicating an effect of terlipressin on SCr in patients with HRS type 1.

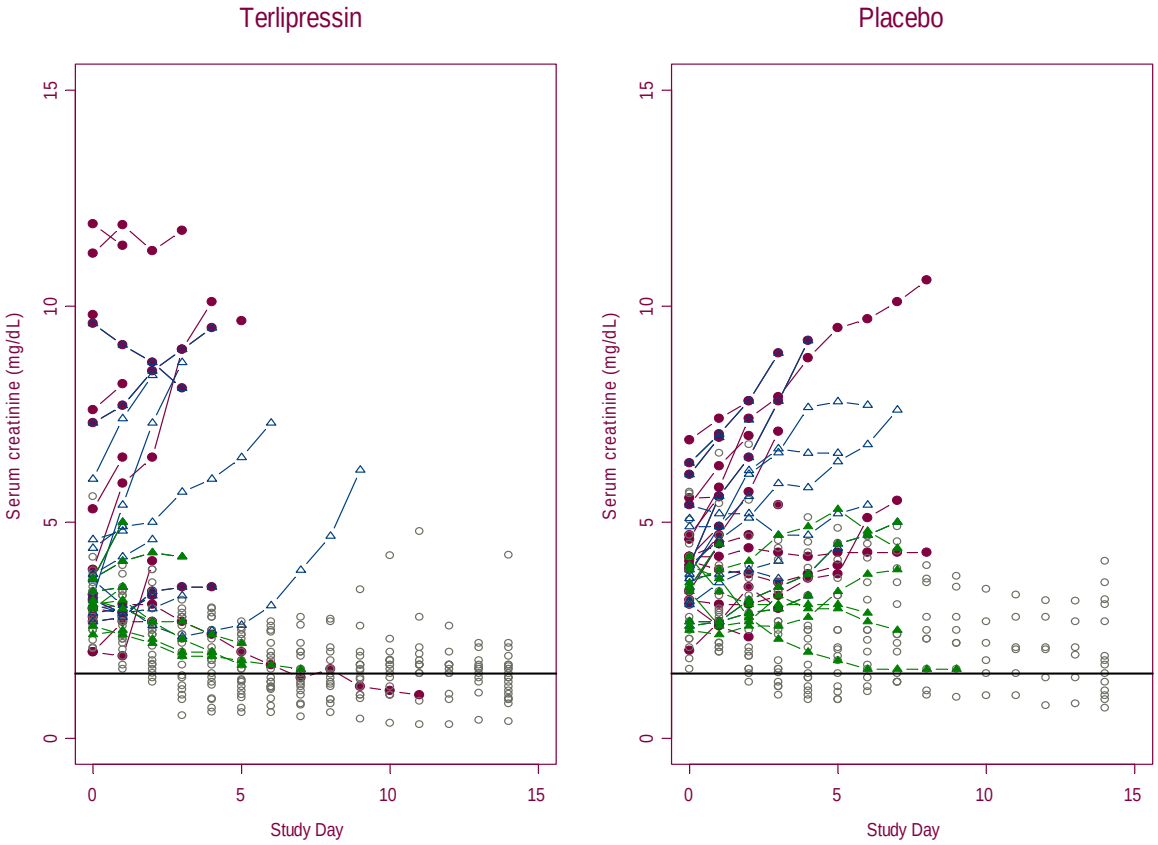


Figure 2: Plot of serum creatinine versus study day for terlipressin treated (n=56) and placebo treated (n=55) subjects in study OT-0401. Serum creatinine profiles are presented by patient disposition ie., study completion (○), death (●), hemodialysis (Δ) or liver transplant (▲). The horizontal solid line represents the threshold serum creatinine value of 1.5 mg/dL. (Data source: Scrmapl.xpt, Dialysis.xpt, transplant.xpt, Change from Baseline Scr.jmp)

However, the relevance of this observed decrease in SCr to below 1.5 mg/dL in HRS type 1 is not clear. The number of deaths in the terlipressin treated group on day 14 were

[5] Results of NCA

similar to that observed in the placebo group (terlipressin = 16, placebo = 17). Similarly, the number of patients who received a liver transplant (terlipressin = 8, placebo = 9) or met criteria for dialysis (terlipressin = 14, placebo = 15) in the terlipressin treated group were similar to that in the placebo group[6]. The decrease in serum creatinine observed in a larger number of patients in the terlipressin treated group as compared to placebo, does not appear to result in a clinically meaningful benefit. Further, the limitations of study OT-0401 (as discussed below) make interpretation of the relevance of a decrease in SCr to HRS type 1 difficult.

3. **Can data from OT-0401 and TAHRS be used to design an informative clinical trial in this population?**

Study OT-0401 failed to meet its primary endpoint. A number of reasons may have contributed to this. A few are listed below and can be modified in future studies.

1. *Duration of treatment:* In study OT-0401, patients were treated for variable number of days after SCr had reached values < 1.5 mg/dL, confounding the interpretation of the observed change in SCr. In future studies patients should be continued on the assigned treatment till the end of study.
2. *Tighter inclusion criteria for SCr:* Six individuals in the terlipressin treated group had baseline SCr above 7 mg/dL (**Figure 2**). This obvious baseline imbalance may have impacted the results of study OT-0401. Modifying the inclusion criteria (doubling of serum creatinine to above 2.5 mg/dL) to include an upper limit for SCr (doubling of serum creatinine to above 2.5 mg/dL but below 7 mg/dL) may result in a more uniform population.

In addition, to enable accurate characterization of PK and exposure – response relationships, blood samples should be collected on study day 1. In OT-0401, PK sampling was performed after study day 3, by when 22 patients from the terlipressin group had discontinued treatment.

Recommendations

1. Proposed labeling (b) (4) (b) (4) is not acceptable.
2. In designing future studies with terlipressin the points discussed above should be considered.

Label statement

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underlined blue font.

(b) (4)

[6] Medical Officer's review, Sponsor's data files (Dialysis xpt, transplant xpt)

(b) (4)

Pertinent regulatory background

Terlipressin (Lucassin®) is a systemic vasoconstrictor being developed by Orphan Therapeutics for use in the management of HRS type 1. HRS is a rare and fatal condition that occurs in patients with end stage liver disease, where changes in the splanchnic circulation caused by the liver disease result in poor blood flow to the kidney and subsequent deterioration of renal function. There are no FDA approved drugs for the treatment of HRS. Hence, terlipressin was granted orphan status in October 2004 and fast track designation in April 2005 (rolling NDA, priority review).

Sponsor's analysis

The sponsor conducted a population pharmacokinetics analysis to characterize the disposition of terlipressin in patients with HRS type 1. A graphical exploratory exposure-response analysis was also conducted.

Population pharmacokinetics

Study OT-0401

Study OT-0401 was a multi-center, randomized, double-blind, placebo-controlled, parallel design study designed to evaluate the safety and effectiveness of terlipressin in treating subjects with HRS type 1. Patients were randomized to receive 1 mg/kg terlipressin administered intravenously every 6h or matching placebo. The dose was doubled to 2 mg/kg given every 6 h after study day 3 in patients whose serum creatinine did not decrease by > 30% of baseline, at the discretion of the investigator.

Pharmacokinetic samples were collected in a subset of 39 terlipressin treated patients according to a sparse sampling strategy based on PK data in healthy subjects [7,8]. A pre-dose blood sample was drawn at baseline, and then two blood samples (one from each block - Block A: 0.083, 0.5, 1, 2 h and Block B: 3, 4, 5, 6 h) were collected on days 3, 6, and/or 9. One additional sample was collected on day 14 or at the end of treatment. Serum creatinine was measured daily till the end of treatment and on study day 14.

Reviewer's comment:

- *According to the protocol 2 samples would be obtained from each patient on multiple occasions (days 3, 6, 9 and end of study), and was judged acceptable to characterize terlipressin PK. However, contrary to the protocol, only 13 patients in the terlipressin treated group had 2 samples collected on more than one occasion.*
- *Twenty two of the 56 patients randomized to receive terlipressin dropped out of the study by day 3. Hence, terlipressin exposure data were not collected in a significant portion of the patients in this study.*

[7] *Fosling et al, J Endocr 1980 (85) : 237-44*
[8] *Nilsson et al, Drugs Exptl Clin Res XVI(6)370*

Data

Of the 174 terlipressin concentrations records collected from 39 patients, 70 records were excluded from analysis as follows. Forty nine samples were below the limit of quantification, eight samples were considered to be outliers, six samples had missing dosing information, six samples were single observations, and one sample was associated with a missing sampling time. Hence, a total of 104 concentration records, collected from 29 terlipressin treated patients were available for analysis and were included in the PK dataset.

Reviewer's comments:

The sponsor deleted 8 data points from PK dataset based on subjective criteria. Further, 3 pairs of data points were switched based on the assumption that they were reported at the wrong time points. Terlipressin concentration data were reported for some patients in the placebo group. These were single points and suggest contamination of the samples. These however, do not impact the estimation of the mean parameters.

Analysis methods

Log-transformed terlipressin concentration versus time data were modeled in NONMEM V, Level 1.1 (Globomax LLC, Hanover, MD), using the first order conditional estimation method for parameter estimation. A two-compartment pharmacokinetic model with first order elimination from the central compartment, parameterized in terms of clearance (CL) and volume of distribution (V), and inter-compartmental distribution (Q) was selected as the base structural model. Random effects were modeled on CL and V1, and assumed to follow a log normal distribution. The random residual error was modeled by an exponential error model (additive on the log scale). The parameter estimates from the base model are presented in **Table 1**.

Table 1: Parameter estimates from the base model. (Ref: Population Pharmacokinetics report, Protocol OT-0401, section 7.4.4)

Parameter	**Point estimate (% CV)**	**Inter-individual variability (%CV)**
CL (L/h)	32.2 (21)	68 (41)
V1 (L)	27.0 (36)	98 (65)
V2 (L)[9]	10 Fixed	-
Q (L/h)[5]	14 Fixed	-
Residual error (proportional)	65% (8.5)	-

Covariate relationships were evaluated following the stepwise forward addition and backward deletion method. The covariates tested are listed in **Table 2**.

[9] Values estimated from healthy subject data presented in *Nilsson et al, Drugs Exptl Clin Res XVI(6)370.*

Table 2: Covariates tested in the population pharmacokinetic analysis. (Ref: Population Pharmacokinetics report, Protocol OT-0401, Table 6.4.6)

Continuous Covariates	Discrete Covariates
Dose	Gender
Age	Age group
Weight	Race
Renal function/creatinine clearance (CRCL)	Hepatic function/Child-Pugh Scores
Hepatic function • AST • ALT • Alkaline phosphatase • Bilirubin	

None of the covariates tested had a significant effect on CL or V1. The base model was therefore also the final model. The goodness of fit plots for the terlipressin PPK model are presented in **Figure 3**.

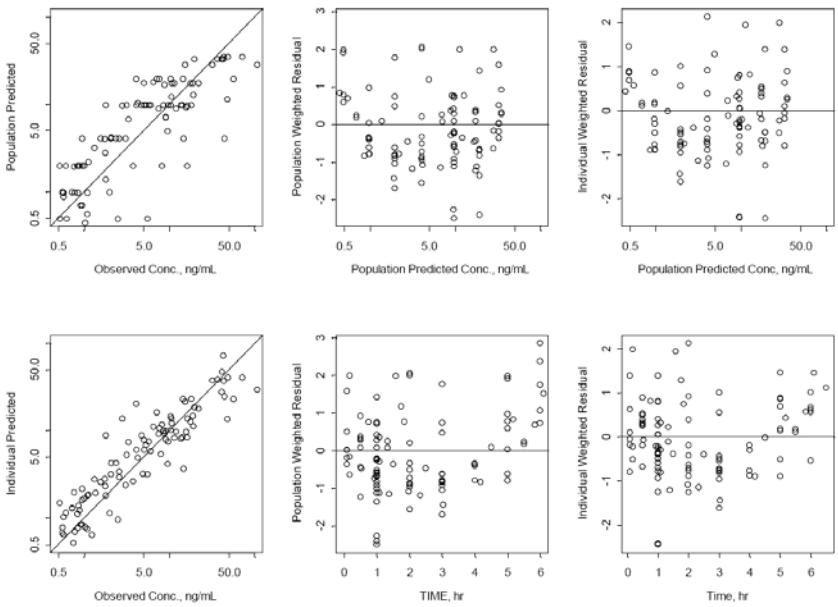


Figure 3: Goodness of fit plots for the final model (Ref: Population Pharmacokinetics report, Protocol OT-0401, attachment 10).

Reviewer's comments:

- *While fixing model parameters to historical values reported in healthy subjects is not optimal, it is acceptable considering the limited data available for characterization.*
- *The magnitude of the residual error in the final model suggests limited utility of the model in making predictions.*
- *Given the small range of patient demographics in study OT-0401, the value of conducting any covariate analysis is doubtful.*

Exposure – response

The sponsor explored potential exposure – response relationships for effectiveness and safety by graphing model predicted exposure (AUC, C_{max} or C_{avg}) against incidence of HRS reversal and serious adverse events. No correlation between exposure and response were apparent.

Reviewer's comment:

- *AUC/C_{max}/C_{avg} were calculated for all treatment days for an individual, and plotted against incidence of treatment success or HRS reversal. Multiple exposure measures for a single individual may have distorted any trends present.*
- *Given that terlipressin is hypothesized to improve renal function, change in serum creatinine may be a more appropriate response variable.*

Reviewer's analysis

The reviewer's PPK analysis results concur with that of the sponsor, and are hence not described here.

Exposure-response

The reviewer conducted limited graphical exploration of the available exposure-response data to address the deficiencies listed above.

Methods

A new dataset was created by merging datasets containing predicted AUC/Cmax/Cavg (source: sponsor's report) and serum creatinine values (source: Scrmapl.xpt, Change from baseline.jmp[10]) for the study duration.

In study OT-0401, terlipressin dose could be doubled if serum creatinine had not decreased by 30% from baseline after 3 days of treatment. Also, if serum creatinine did not decrease or rose above basline after 7 days of treatment, this was counted as treatment failure. Hence, study days 3 and 7 were considered relevant for this exploratory analysis.

Results

Plots of change from baseline serum creatine versus exposure are presented in **Figure 3**.

[10] Obtained from the medical officer.

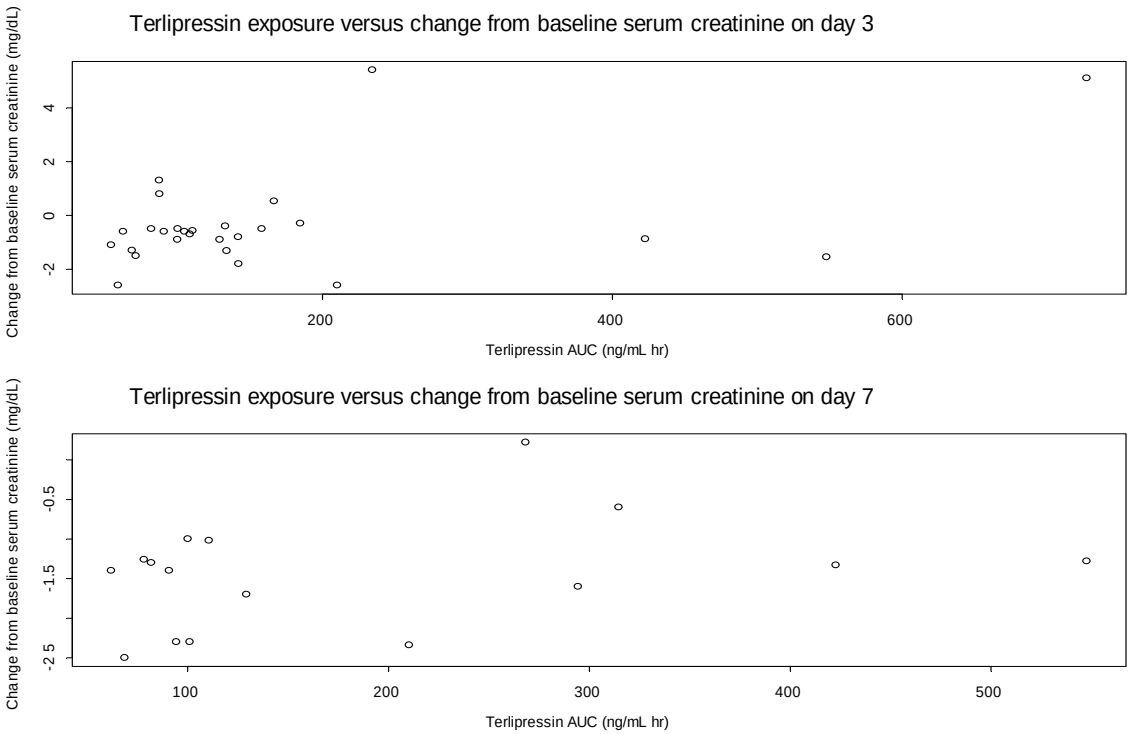


Figure 3: Plot of terlipressin AUC versus change from baseline in serum creatinine on day 3 (top panel) and day 7 (bottom panel). (Data source: sponsor's PPK analysis results, Scrmapl.xpt, Change from baseline.jmp)

As seen in **Figure 3**, no correlation between exposure and response were apparent on study days 3 or 7. However, because of the limitations of the study, these results cannot be interpreted as a lack of any relationship between exposure and serum creatine in HRS type 1, and are therefore inconclusive.

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22231	ORIG 1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIVYA MENON ANDERSEN
08/27/2009

PRAVIN R JADHAV
08/27/2009

RAJANIKANTH MADABUSHI
08/27/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA NUMBER:	22,231
DATE RECEIVED BY CENTER:	January 30, 2009
DRUG PRODUCT:	LUCASSIN® Injection
DRUG SUBSTANCE:	Terlipressin diacetate pentahydrate
INTENDED CLINICAL POPULATION:	Patients with hepatorenal syndrome (HRS) type 1
SPONSOR:	Orphan Therapeutics, LLC
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	G. Jagadeesh, Ph.D.
PHARM/TOX SUPERVISOR:	Charles Resnick, Ph.D.
DIVISION DIRECTOR:	Norman Stockbridge, M.D., Ph.D.
PROJECT MANAGER:	Anna Park

Date of review submission to Division File System (DFS):

NDA number: 22,231
Date of Submission: 01-28-2009
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Sponsor: Orphan Therapeutics, LLC
Manufacturer of Drug Substance: (b) (4) (b) (4)

Reviewer: G. Jagadeesh, Ph.D.
Division: Division of Cardiovascular and Renal products
Review completion date: July 30, 2009

Drug Product: Lucassin® injection
Drug Substance

Generic name: **Terlipressin**, Triglycyl lysine vasopressin, Glypressin
Chemical name: N-(N-(N-glycyl-glycyl)- glycyl)-8-L-lysine-vasopressin, 1-triglycyl-8-lysine-vasopressin
CAS registry number: 14636-12-5
Molecular formula/molecular weight: $C_{52}H_{74}N_{16}O_{15}S_2$ / 1227.4 (free base)

H-Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2
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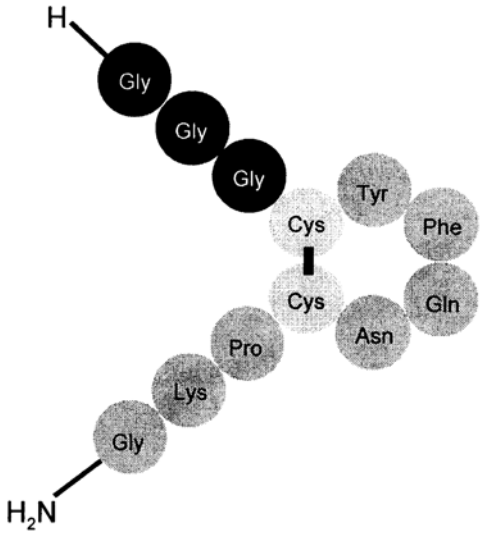

IND Under Which Clinical Trials Were Conducted: 68,582
Drug Class: Vasopressin receptor agonist
Indication: Hepatorenal syndrome (HRS) type 1
Clinical Formulation: LUCASSIN® is provided as a sterile, lyophilized powder in a clear glass vial for intravenous administration; mannitol is used (b) (4) Acetic acid is used to adjust pH during manufacture. Each vial must be reconstituted with 5 ml 0.9% NaCl for injection. Each vial of LUCASSIN® contains 0.85 mg terlipressin free base, equivalent to 1 mg terlipressin acetate.
Route of Administration: Intravenous bolus injection
Proposed Dosage Regimen: The starting dose is 1 mg every 6 hours (4 mg/day) by slow intravenous bolus injection. If, after 3 days, serum creatinine has not decreased by at least 30% from the baseline value, it is recommended that the dose be doubled to (b) (4) mg every 6 hrs (b) (4) mg/day).
Disclaimer: Unless indicated otherwise, tables and graphs (some with editorial corrections by the reviewer) are taken directly from the sponsor's submission.

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EXECUTIVE SUMMARY

I. Background

Terlipressin is a synthetic 12 amino acid peptide. It differs from endogenous arginine vasopressin (AVP) by the substitution of 'lysine' for 'arginine' at the 8th position of the endogenous molecule and the addition of three 'glycyl' residues at the amino terminus. Terlipressin is a systemic vasoconstrictor with effects mediated through vasopressin V_1 receptors (V_1R).

V_1R are found on vascular smooth muscle cells and cardiomyocytes and modulate blood vessel vasoconstriction and myocardial function. Stimulation of V_1R in the splanchnic arterial vessels reduces blood flow to and lowers blood pressure in the portal system. This attenuates bleeding in esophageal varices. Platelets express V_1R, which upon stimulation induce an increase in calcium, facilitating thrombosis. Thus, AVP agonists (including terlipressin) are used in many countries outside the USA for the treatment of esophageal variceal hemorrhage (EVH).

The current application is for the use of terlipressin for the treatment of hepatorenal syndrome (HRS) type 1. Typically, patients with HRS type 1 are in their late fifties, predominantly male and have a history of mostly alcohol-related liver cirrhosis with ascites. Two types have been described. Type 1 is characterized by rapid deterioration of renal function (very low renal perfusion and glomerular filtration rates), with a marked increase in serum creatinine (>2.5 mg/100 ml), azotemia, low urine output, and marked sodium retention, with a median survival time of less than 2 weeks.[a] Type 2 is a more stable form with less severe renal failure and longer survival, typically in patients with a relatively preserved liver function. The likely pathogenic mechanism leading to HRS is a vasoconstriction of the renal circulation secondary to a marked arterial vasodilation in the splanchnic vascular bed leading to reduction in effective arterial blood volume which leads to homeostatic activation of vasoconstrictors such as norepinephrine and neuropeptide Y which are co-stored within the sympathetic nerves.[b]

Several clinical studies have demonstrated that terlipressin is effective in reversing HRS. Activation of V_1 receptors concentrated in the splanchnic region decreases splanchnic blood flow and thereby reduces blood flow to the portal system and consequently attenuates portal pressure or intrahepatic vascular resistance. It is hypothesized that terlipressin-induced vasoconstriction in the splanchnic area results in increased renal blood flow and improved renal function *via* a complex and not yet fully understood suppression of the activity of the renin angiotensin

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[a] Lowe, R.C. and Grace, N.D.: Pharmacologic therapy for portal hypertension. Curr Gastroenterol Rep 3: 24-29, 2001.
Lebrec.: Drug therapy for portal hypertension. Gut 49: 441-12, 2001.
Patch, D.L.: Review article: pharmacological treatment of the hepatorenal syndrome in cirrhotic patients. Alim Pharmacol Therap 14: 515-21, 2000.

[b] Arroyo, V. et al. Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. J Hepatol 32 (Suppl 1): 157-70, 2000.
Arroyo, V. et al. Hepatorenal syndrome in cirrhosis: pathogenesis and treatment. Gastroenterol 122: 1658-76, 2002.
Uriz, J. et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 33: 43-48, 2003.

aldosterone system, the sympathetic nervous system and the renal prostaglandins.[b] Furthermore, stimulation of V_1 receptors on the efferent arterioles increases renal perfusion pressure and glomerular filtration rate.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

B. **Recommendations for Additional Nonclinical Studies:** None

C. **Recommendations for Labeling:** The sections of the proposed labeling (updated May 1, 2009) that deal with nonclinical studies are considered satisfactory with the following exception.

(b) (4)

III. Summary of Nonclinical Findings

With the exception of hemolysis and effects on cytochrome P450 enzymes, the sponsor has not conducted pharmacology or pharmacokinetic studies (*in vitro* or *in vivo*) on terlipressin. They have relied on studies that have been extensively described in the literature and by the well known profile of vasopressin (AVP) described in the literature.

Both in animals and humans, terlipressin is metabolically converted to an active product, lysine vasopressin. Both are rapidly eliminated, necessitating frequent doses (every 6 hr). Similar doses of terlipressin (on a weight basis) elicit hemodynamic effects in rats (2 to 90 µg/kg), dogs (20 to 100 µg/kg) and humans (7.5 to 30 µg/kg). The mean half-life estimates for terlipressin and lysine vasopressin in animals are approximately 0.2 hr and 2 hr, respectively, which are similar to those observed in HRS patients.

A. **Brief Overview of Toxicology:** Single dose intravenous toxicity studies were conducted in mice and rats, and repeat dose intravenous toxicity studies were conducted in rats and dogs. Based on mortality and clinical signs, the dog (MTD 0.3

mg/kg) was considered to be more sensitive than the rat (MTD 2 mg/kg), while the mouse was the least sensitive (MTD 500 mg/kg). Deaths in rats were due to severe vasoconstriction resulting in reduced perfusion, pulmonary congestion and inflammation of the lungs. Most rat deaths occurred on the first day of dosing and were dose-dependent. In rats and mice, clinical signs such as lethargy, dyspnea, hyperapnea, ataxia and hind-leg paralysis were noted. Onset of clinical signs was rapid, and they resolved over a short time period. Splitting the daily doses into two decreased the intensity and incidence of clinical signs and mortality.

Daily administration of terlipressin diacetate pentahydrate to rats (0.15 or more mg terlipressin/kg/day) and dogs (0.0625 or more mg terlipressin/kg/day) for 28 days resulted in a moderate decrease in body weight gain of male rats relative to control. A non-dose-dependent decrease in mean absolute kidney weight was noted for male rats and male dogs at all doses. This was accompanied by histopathological changes in the kidneys (multifocal chronic cortical nephritis, interstitial lymphocytic infiltration and/or tubular dilatation) for both male and female dogs and rats and was dose-related. Males generally appeared to be more sensitive to terlipressin toxicity than females, though there was no difference in systemic exposure between males and females. In rats (but not dogs) there was a decrease in testes weight at 0.5 or more mg terlipressin/kg/day that correlated with seminiferous tubular degeneration. Both kidney and testes findings were absent in control animals and were not fully resolved by the end of the 2 week recovery period. A no observed adverse effect level was not established for either rats or dogs.

Terlipressin has no mutagenic or clastogenic activity. No carcinogenicity or reproductive toxicity studies were performed. Literature provides evidence of human fetal risk due to increased uterine contractility and reduced blood flow to the uterus and placenta.

B. Other Preclinical Studies

Since terlipressin is given by direct intravenous injection in the clinic, an *in vitro* study of red cell fragility was conducted. In this study, terlipressin had no significant effect on human red cell fragility and produced no hemolysis. *In vitro* studies have demonstrated that terlipressin does not inhibit or induce the activity of any of the human cytochrome P450 isoenzymes studied.

C. Nonclinical Safety Issues Relevant to Clinical Use

The clinical signs and toxicity noted in toxicology studies are generally consistent with pharmacologic effects of terlipressin and correlated with dose. At the dose of terlipressin used to treat HRS patients, the strong V_1R-mediated vasoconstrictor activity is the pharmacodynamic mechanism responsible for its clinical activity. These V_1R-mediated effects are also responsible for many of the adverse effects observed in both nonclinical and clinical studies. The major organ systems affected by terlipressin in the rat and dog studies were lung, kidney and testes, as evidenced by

gross necropsy and/or histopathological findings. Additionally, dose-related inflammation was noted at the injection site.

The pharmacological activity of terlipressin is similar in humans and the species used in the safety evaluation studies and, according to the sponsor, the animals and humans respond to similar concentrations of terlipressin. Systemic exposure data from the toxicity studies in animals and systemic exposure data for humans are, however, inadequate for establishing safety margins for the adverse effects observed in animals. When comparisons are based on body surface area adjusted dose levels, the lowest terlipressin dose level studied in rats (LOAEL dose) was about 1-2 times higher than that studied in HRS patients (1-2 mg). In dogs, the lowest dose studied (LOAEL dose) was 0.7 to 1.5 times that studied in HRS patients. Though there is little if any safety margin for the adverse findings observed in dogs and rats, the short half-life (approximately 1 hr) and duration of therapy (14 days), and the extensive, published clinical experience with this drug suggest that terlipressin can be used safely for the treatment of HRS type1 at the proposed therapeutic dose in accordance with the proposed product labeling.

PHARMACOLOGY/TOXICOLOGY REVIEW

1.0. PHARMACODYNAMICS

1.1. Effect of Terlipressin on Human Red Cell Fragility *In Vitro*

This study (#CB04-5046-EV-PA) was conducted in compliance with the GLP regulations. It was initiated on February 19 and completed on March 19, 2004. It was performed at (b) (4) (b) (4) under subcontract from (b) (4) The objective of the study was to evaluate the effect of terlipressin on human red blood cells *in vitro* at clinically relevant concentrations.

Whole blood was collected from 5 male and 5 female adult human volunteers. Each specimen was divided into 5 aliquots and incubated with control (none, saline) and terlipressin acetate (17, 57 and 170 ng/ml, expressed as terlipressin). The samples were incubated in duplicate at 37°C (except control, which was incubated at room temperature) for 30 min. The samples were then centrifuged and the supernatants analyzed for hemoglobin concentration.

Terlipressin did not have a statistically significant effect on the hemoglobin concentration in either males (p=0.116) or females (p=0.221) at concentrations of up to 170 ng/ml (Table 1.1.1) suggesting no effect on red cell fragility.

TABLE 1.1.1
EFFECT OF TERLIPRESSIN ON MEAN CONCENTRATION OF PLASMA HEMOGLOBIN (MG/100 ML) IN ADULT HUMAN VOLUNTEERS

Sex	Control		Terlipressin, ng/ml, incubated at 37°C		
	None, RT	Saline, 37°C	17	57	170
Male	10.3	11.8	12.9	11.3	12.5
Female	6.2	7.2	7.1	6.8	6.3

2.0. POTENTIAL FOR DRUG INTERACTIONS

2.1. Determination of the Inhibitory Potential of Terlipressin on P450 Enzymes in Human Liver Microsomes

This non-GLP study (#302-1173) was conducted at (b) (4)
The experiments were conducted between January 25 and March 22, 2006.

The objective of the study was to determine the potential of terlipressin diacetate pentahydrate to inhibit the activities of cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in human liver microsomes.

Methods

Microsomes prepared from liver homogenates pooled from at least 10 human donors (sex not identified) were incubated with terlipressin diacetate pentahydrate and a selective substrate for each CYP isoform at 37°C. The formation of the selective metabolite from its substrate was measured by high-performance liquid chromatography. Catalytic activities of the microsomes for different P450 isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) were measured in the presence of isoform-selective substrates specific to an enzyme (Table 2.1.1). Terlipressin diacetate pentahydrate (lot #05RD53) was dissolved in water and tested at concentrations ranging from 10 to 5000 ng/ml.

Results

Terlipressin diacetate pentahydrate did not inhibit any of the measured CYP-dependent activities at concentrations up to 5,000 ng/ml.

TABLE 2.1.9.1
INHIBITION OF HUMAN P450 ISOFORMS BY ALISKIREN

P450 enzyme	**Specific Enzyme**	**Substrate**	**Metabolite formed**
CYP1A2	Phenacetin *O*-deethylase	Phenacetin	Acetaminophen
CYP2A26	Coumarin 7-hydroxylase	Coumarin	7-hydroxycoumarin
CYP2B6	*S*-mephenytoin N-demethylase	*S*-mephenytoin	Nirvanol
CYP2C8	Paclitaxel 6-hydroxylase	Paclitaxel	6-hydroxypaclitaxel
CYP2C9	Tolbutamide 4'-methyl hydroxylase	Tolbutamide	4'-methylhydroxytolbutamide
CYP2C19	S-mephenytoin 4'-hydroxylation	*S*-mephenytoin	4'-hydroxymephenytoin
CYP2D6	Dextromethorphan *O*-demethylase	Dextromethorphan	Dextrorphan
CYP2E 1	Chlorzoxazone 6- hydroxylase	Chlorzoxazone	6-hydroxychlorzoxazone
CYP3A4	Testosterone 6ß-hydroxylase	Testosterone	6ß-hydroxytestosterone

2.2. Evaluation of the Induction Potential of Terlipressin on P450 Enzymes in Human Hepatocytes

This non-GLP study (#302-1172) was conducted at (b) (4)
The experiments were conducted between February 27 and March 11, 2006.

The objective of the study was to evaluate the potential of terlipressin diacetate pentahydrate to induce the activities of cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in human hepatocytes following *in vitro* exposure.

Methods

Hepatocytes prepared from fresh liver tissue from 3 human female donors were incubated with terlipressin diacetate pentahydrate for 48 ± 3 hr at 37°C. The incubation mixture was washed with fresh medium free of test substance and incubated with solution containing a selective substrate for each CYP isoform (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) for 4 hr at 37°C. Incubation was terminated by adding ice-cold methanol. The CYP-dependent rates of formation of metabolites from its substrate for different P450 isoforms was measured by high-performance liquid chromatography or LC/MS. Terlipressin diacetate pentahydrate (lot #05RD53) was dissolved in water and tested at concentrations ranging from 10 to 5000 ng/ml.

Results

Terlipressin diacetate pentahydrate, up to a concentration of 5,000 ng/ml, did not induce the activities of any CYP isoforms. Known CYP inducers produced induction of CYP1A2 and CYP3A4 activity demonstrating the responsiveness of the hepatocytes to CYP inducers.

3.0. TOXICOLOGY

3.1. Single Dose Toxicity

3.1.1. Intravenous Toxicity Study in Mice

This GLP study (AB25XV.123 (b) (4)) was conducted by (b) (4) between March 15 and April 13, 2006. It was conducted as a supporting study for a micronucleus test. For experimental details, see Section 3.3.3. In summary, 6 to 8 week old male and female mice (ICR from Harlan; weight: 22.1 to 34.20 gm) received a single intravenous dose of terlipressin (20, 500, 600, 750 or 1000 mg/kg; 10 ml/kg; n=5/sex/dose). Terlipressin diacetate pentahydrate (lot #V125/165-111, 98.4% pure) was dissolved in 0.9% sodium chloride for injection. All animals were observed for 3 days for clinical signs of toxicity. Body weights were recorded before dose administration, and 1 and 3 days post dose.

All males and females receiving at 750 or more mg/kg died; 2 males and a female died at 600 mg/kg; and a male at 500 mg/kg. Lethargy was noted in all males and females at 20 or more mg/kg. Piloerection was observed in all males receiving 500 or more mg/kg. Hyperactivity, vocalization and excessive grooming were noted in all animals receiving 500 or more mg/kg. Convulsions were seen in all animals receiving 750 or more mg/kg (Table 3.1.1.1). According to the sponsor, the MTD was 500 mg/kg.

TABLE 3.1.1.1
CLINICAL SIGNS AND MORTALITY FOLLOWING A SINGLE INTRAVENOUS DOSE OF TERLIPRESSIN DIACETATE PENTAHYDRATE IN ICR MICE

		Number of Animals With Observed Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
Treatment (10 mL/kg)	**Observation**	**Males**	**Females**	**Males**	**Females**
Terlipressin Diacetate Pentahydrate 20 mg/kg	Lethargy	5/5	5/5	0/5	0/5
500 mg/kg	Lethargy	5/5	0/5	1/5	0/5
	Piloerection	5/5	0/5		
	Hyperactivity	5/5	5/5		
	Vocalization	5/5	5/5		
	Excessive grooming	5/5	5/5		
600 mg/kg	Lethargy	4/5	4/5	2/5	1/5
	Piloerection	4/5	0/5		
	Hyperactivity	5/5	5/5		
	Vocalization	5/5	5/5		
	Excessive grooming	5/5	5/5		
750 mg/kg	Convulsions	5/5	5/5	5/5	5/5
1000 mg/kg	Convulsions	5/5	5/5	5/5	5/5

3.2. Repeat Dose Toxicity

3.2.1. 7 Day Intravenous Study in Rats

Key Study Findings: Four of nine males and 2 of 9 females receiving a single dose of 2 mg terlipressin/kg died within an hour of dosing. A statistically significant reduction in mean body weight gain relative to control was noted for males receiving this dose intravenously for 7 consecutive days. Renal tubular nephrosis and interstitial fibrosis and inflammation of the kidneys were noted in all females and in 1 of 5 males receiving the 7 day treatment. Mild thymic depletion and degeneration of the testicular seminiferous tubules were also noted as being treatment-related.

Study No.: CB05-5121-R-TX
Location of Report: Module 4, Vol 4 of 14
Conducting Laboratory and Location: (b) (4)
Dates of Study: The animals were dosed on Sept 21 and November 1, 2005; necropsied on November 8, 2005.
GLP Compliance: Yes
QA'd Report: Yes
Drug, Lot #: Terlipressin diacetate pentahydrate, #2K05020B supplied by (b) (4) (b) (4) Net peptide content was 82% and concentrations were expressed as anhydrous free base.
Formulation: Terlipressin diacetate pentahydrate was dissolved in sodium chloride for injection and prepared fresh daily.
Animals

Species/Strain: (b) (4) albino (b) (4) rats (*Rattus norvegicus*) obtained from (b) (4) This strain is considered equivalent to the Sprague Dawley strain.
#/Animals/Group: See Table 3.2.1.2.
Age: 6 weeks old at initiation of dosing
Weight: Males: 135-215 gm, Females: 140-165 gm, at initiation of dosing
Husbandry: Animals of the same sex and same dosing group were housed in pairs. Food and water were available *ad libitum*.

Dosing

The study consisted of 2 parts. Part A consisted of a series of 'step-up, step-down' experiments aimed at defining the MTD. Initially, groups of 1 to 6 rats/sex were administered a single dose, 8 or 16 mg/kg, of the test substance (5 ml/kg bolus), via a tail vein, and observed for approximately 1 hr. In a confirmatory study, 6 males and 6 females were administered the estimated MTD of 8 mg/kg, i.v., and observed for 3 days. Due to male mortality, the doses were titrated down to 4 and then to 2 mg/kg. The sponsor considered 2 mg/kg to be the MTD though there were deaths at this dose.
In part B, 2 groups of 6 male and 6 female rats and a satellite group of 3 male and 3 female rats (for toxicokinetics study) were given a single daily i.v. dose of 2 mg terlipressin/kg or vehicle for 7 consecutive days (Table 3.2.1.2). Control animals received the vehicle.

Observations and Measurements

Except for clinical signs and mortality, all findings were recorded only for animals dosed continuously for 7 days.

Clinical Signs: All animals were observed once daily for clinical signs and mortality.
Body Weight: Recorded on day 0 and at necropsy.
Food Consumption: Not measured.
Hematology[1] and Clinical chemistry[2]: Blood samples were collected at the end of the treatment from all surviving animals.
Pathology: Animals were not fasted prior to terminal necropsy. For part A, a gross necropsy with preservation of gross lesions was done. For part B, a gross necropsy followed by preservation of protocol-specified organs/tissues for histopathological evaluation was conducted on all animals sacrificed at the end of the study (Table 3.2.1.1).

TABLE 3.2.1.1
TISSUES SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

adrenal glands	ileum,	pituitary $^{\pi}$
brain $^{\pi}$	injection site	rectum
cecum	jejunum	spleen $^{\pi}$
colon	kidneys $^{\pi}$	stomach
duodenum	liver $^{\pi}$	testes $^{\pi}$
epididymides $^{\pi}$	lungs	thymus $^{\pi}$
eyes with optic nerves $^{\pi}$	macroscopic lesions	thyroid with parathyroid $^{\pi}$
heart $^{\pi}$	ovaries	

$^{\pi}$: Organ weighed

Toxicokinetics: Blood samples for determination of levels of terlipressin and lysine vasopressin were planned to be collected from the satellite group of 3 male and 3 female rats on study day 0 (1st dose) and day 6 (7th dose) at 15, 30, and 60 min after dosing. However, the collection was not successful because of difficulty in collecting the blood due to the vasoconstrictive effect of terlipressin. Some of the animals died during the procedure on day 0 and replacement animals were added. Few collections were made on day 0 and 6. Thus, the results are not discussed.

Results

Clinical Signs and Mortality: *Part A (Single dose study):* One male and one female rat receiving 8 mg terlipressin/kg exhibited lethargy and dyspnea within a few minutes of dosing. After about 5 min, both animals became ataxic and exhibited open-mouth gasping. This was followed by temporary paralysis of hind legs. Both animals had fully recovered 1 hr post dose. This led the sponsor to dose, on the same day, a male and a female at 16 mg/kg. This dose resulted in similar clinical signs followed by uncoordinated movements and high-leg paralysis in both animals. The animals began

[1] erythrocytes, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, white blood cell differential, platelets.
[2] ALT, AST, AP, total bilirubin, total protein, albumin, globulins, A/G ratio, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol

bleeding from the nose about 12 min post dose and died 14 min post dose. In order to confirm the estimated MTD of 8 mg/kg, 2 additional rats of each sex were given 8 mg terlipressin/kg. Similar clinical signs were noted and the animals recovered by 30 min post dose. No further clinical signs were noted in these animals until sacrificed on day 3.

Two weeks later, 6 male and 6 female rats were dosed at 10 mg/kg (see Table 3.2.1.2). Similar signs were observed in all 12 animals. One male died 15 min and 2 males died 60 min post dose. Necropsy showed mottled kidneys and discolored lungs. All 6 females survived. After a week, 6 additional rats of each sex were dosed at 8 mg/kg and observed for 3 days. Similar clinical signs were observed for all animals. Three males died within 30 min of dosing. No necropsy done. All the surviving animals were sacrificed on day 3 to reveal mottled kidneys in 2 animals.

Since 8 mg/kg was not tolerated, 6 male rats were dosed at 4 mg/kg and observed for 3 days. Similar signs were noted and 4 animals died 10 to 52 min after dosing. The remaining animals recovered. Necropsy was not performed. The effects of the 4 mg/kg dose were confirmed in 6 additional males. All exhibited similar clinical signs and 2 died within 34 min of dosing. The remaining animals recovered. A lowered dose of 2 mg/kg was given to 6 males. Similar clinical signs were noted and one rat died within a few minutes of doing. Remaining animals recovered and showed no further clinical signs. Despite the one death, the sponsor concluded that the MTD in male rats was 2 mg/kg. Mortality (for both part A and part B) is summarized in Table 3.2.1.2.

Part B: In the 7-day study, one treated male rat died approximately 40 min after the first dose and no necropsy was done. In all of the animals, clinical signs (lethargy, dyspnea, hyperpnea, ataxia and hind-leg paralysis) were noted after each dose. Recovery was noted within 1 hr of dosing. In the toxicokinetics group, all males and 2/3 females died on first day blood sampling. Consequently replacement animals (2 M and 1 F) were added. One replacement male died during blood sampling. No necropsy was done in the toxicokinetics group.

Body Weights: Mean body weights and body weight gain were lower than control for treated males ($p < 0.05$) at the end of the 7 day treatment.
Hematology: Statistically significant decreases in erythrocyte counts, hemoglobin concentrations and hematocrit relative to control were noted in females treated with terlipressin.
Clinical Chemistry: A small (<2-fold) but statistically significant increase in ALT relative to control was noted in females receiving terlipressin.

TABLE 3.2.1.2
MORTALITY

Part	Start date	Group #	No. and sex	Terlipressin mg/kg, iv	# of doses	Mortality
A	9/21/05		4 M	8	Single dose	0
			3F	8		0
			1 M	16		1
			1 F	16		1
	10/4/05		6 M	10		3
			6 F	10		0
	10/11/05		6 M	8		3
			6 F	8		0
	10/14/05		6 M	4		4
	10/20/05		6 M	4		2
	10/27/05		6 M	2		1
B	11/1/05	1	6 M/6 F	0 (vehicle)	7	
		2	6 M/6 F	2	7	1 M
		3 (TK)	3 M/3 F	2	7	3 M/2 F

Organ Weights: Statistically significant decreases in kidney, testes, thyroid/parathyroid and thymus weights (both absolute and relative to body weight) relative to control were noted in terlipressin-treated males. In females, a statistically significant increase in absolute and relative liver weight relative to control was noted.
Gross Pathology: The macroscopic lesions noted in the kidneys correlated with the histopathologic findings.
Histopathology: Significant findings were noted in the kidney, testes and thymus. Mild to moderate to severe acute tubular nephrosis, with interstitial inflammation and fibrosis, probably ischemic in origin was noted in 1 of 5 males and 5/6 females receiving terlipressin. In the testis, mild to moderate seminiferous tubular degeneration was noted in 4/5 males. In the thymus, mild cortical lymphoid depletion was noted in 3/6 females.

3.2.2. 28 Day Intravenous Study in Rats with a 14 Day Recovery

Key Study Findings: A total of 27 drug treated animals (23 males, 4 females) died during the study; mortality was dose-dependent. Except for 2 animals, all deaths occurred on study day 0 or 1. The main clinical signs were pale body color, lethargy, labored breathing and loss of function of the rear legs. A **s**tatistically significant reduction in mean body weight gain relative to control was noted for males receiving 0.15 or more mg/kg/day. Chronic nephritis, ischemic in origin, was noted in both sexes receiving 0.5 or more mg/kg/day. Mild cortical lymphoid depletion and perivascular inflammation at the injection site was noted in all drug-treated groups. Degeneration of the testicular seminiferous tubules was observed in males receiving 0.5 or more mg/kg/day. A NOAEL was not determined in the study.

Study No.: CB06-5013-R-TX
Location of Report: Module 4, Vol 5 of 14
Conducting Laboratory and Location: (b) (4)
Dates of Study: The animals were dosed on March 13; last necropsied on April 28, 2006.
GLP Compliance: Yes
QA'd Report: Yes
Drug, Lot #: Terlipressin diacetate pentahydrate, #V125//165-111 supplied by (b) (4) Net peptide content was 82% and concentrations were expressed as anhydrous free base.
Formulation: Terlipressin diacetate pentahydrate was formulated in sterile saline for injection and prepared fresh daily. Two representative solutions prepared in two different weeks were frozen at -80°C for dose analysis. Dosing solutions had actual concentrations within 10% of their nominal concentration.
Animals
Species/Strain: (b) (4) albino (b) (4) rats (*Rattus norvegicus*) obtained from (b) (4) This strain is considered equivalent to the Sprague Dawley strain.
#/Animals/Sex/Group: 10 for main study toxicology; 5 for recovery; 9 for toxicokinetics. See Table 3.2.2.1 for details.
Age: 6 weeks old at initiation of dosing
Weight: Males: 210-265 gm, Females: 155-195 gm, at initiation of dosing
Husbandry: Animals were housed singly in plastic cages. Food and water were available *ad libitum*.
Dosing
Doses: In the main toxicology study, 4 groups of 30 rats each were dosed at 0, 0.15, 0.5, or 1.5 mg/kg/day for 28 consecutive days. Due to extensive mortality noted in the high dose group on day 0, the dose was split into two daily doses (0.75 mg/kg/day administered 1 to 2 hr apart), starting on day 1 for the main study groups and day 5 for the toxicokinetics groups. On day 28, 20 rats (10 males and 10 females) from each group were sacrificed. The remaining 5 rats/sex/group were maintained for an additional 14 days and received no drug ('recovery' groups). These animals were sacrificed on day 42. Concurrently, 3 satellite groups of 9 males and 9 females/dose were dosed at 0.15, 0.5 or 1.5 mg/kg/day for 28 consecutive days. As in the main toxicology study, the high dose group animals received two daily doses.

Route, Mode and Duration of Administration: Intravenously (bolus, 5 ml/kg) *via* a tail vein. Control animals received the vehicle.

TABLE 3.2.2.1
STUDY DESIGN

Group	Dose (mg/kg/day)	Number of Rats (M/F)	Number of Replacement Rats due to Mortality[a] (M/F)	Purpose
1	0	10M / 10F	0	Treatment (Day 28)
		5M / 5F	0	Recovery (Day 42)
2	0.15	10M / 10F	0	Treatment (Day 28)
		5M / 5F	0	Recovery (Day 42)
3	0.5	10M / 10F	4M	Treatment (Day 28)
		5M / 5F	0	Recovery (Day 42)
4	1.5[b]	10M / 10F	3M / 1F	Treatment (Day 28)
		5M / 5F	1M / 1F	Recovery (Day 42)
5	0.15	9M / 9F	1M	Toxicokinetics
6	0.5	9M / 9F	2M	Toxicokinetics
7	1.5[b]	9M / 9F	4M / 1F	Toxicokinetics

a : There were not enough spare rats to replace all of the dead males in Group 4
b : Administered as 2 daily doses of 0.75 mg/kg from Day 1 (Group 4) or Day 5 (Group 7)

Observations and Measurements

Except for clinical signs and mortality all other measurements were recorded only for toxicology group animals.

Clinical Signs: All animals were observed during the first hour of post dosing for overt signs of toxic and once daily for clinical signs and mortality.

Body Weight: Recorded on first day of dosing and once weekly during the course of study, and at necropsy.

Food Consumption: Twice daily during the course of study.

Ophthalmology: Conducted prior to study and at necropsy.

Hematology[1] and Clinical chemistry[2]: Blood samples were collected at necropsy from all surviving animals including recovery group.

Urinalysis[3]: Determined at necropsy from all surviving animals including recovery group.

Pathology: Animals were fasted overnight prior to terminal necropsy. Animals in the treated and recovery groups were euthanized on day 28 and day 42, respectively. No necropsy was done on surviving toxicokinetics group animals. No histopathology was done on animals that died during the study. Protocol specified organs were weighed and tissues collected for histopathological evaluation. Microscopic examination was performed on all tissues listed in Table 3.2.2.2 from all animals in the control and high dose groups (both treatment and recovery groups). Target organs were examined from all animals in the mid and low dose groups.

[1] erythrocytes, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, white blood cell differential, platelets, prothrombin time, activated partial thromboplastin time

[2] ALT, AST, AP, total bilirubin, total protein, albumin, globulins, A/G ratio, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol

[3] Color, specific gravity, pH, microscopic examination of sediment, bilirubin, blood glucose, ketones, protein, urobilinogen, creatinine, calcium, phosphorous, potassium, sodium

TABLE 3.2.2.2
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenal glands (paired)*	Oviducts (paired)
Aorta (thoracic)	Pancreas
Bone (sternum, femur)	Pharynx
Bone marrow (femur, sternum, b m smear)	Pituitary gland*
Brain (cerebrum, cerebellum, mid-brain)*	Prostate
Cecum	Rectum
Colon	Salivary gland
Duodenum	Sciatic nerve
Epididymis	Seminal vesicles
Esophagus	Skeletal muscle
Eyes w/optic nerve	Skin and subcutis (inguinal)
Heart (including auricles and septa)*	Spinal cord – cervical
Injection site	Spleen*
Ileum	Stomach
Jejunum	Testes (paired)*
Kidneys (paired)*	Thymus*
Larynx	Thyroid (incl. parathyroid)
Lacrimal gland/Harderian gland	Tongue
Liver (2 lobes)*	Trachea
Lungs with bronchi	Uterus/Cervix
Lymph nodes (mesenteric, mandibular)	Vagina
Mammary gland (inguinal)	Macroscopic lesions
Ovaries (paired)*	

*: Organ weight obtained

Toxicokinetics: Blood samples for determination of levels of terlipressin and lysine vasopressin were collected from the satellite groups on study day 0 (1st dose) (from the tail vein) and day 27 (28th dose) (by cardiac puncture) at 5, 15 and 30 min, and 1, 2, 4, 8 and 24 hr after dosing (3 rats/sex/time point). The collection of blood was not successful after the 1st dose due to the vasoconstrictor effect of terlipressin and deaths in dosed animals.

Results

Analysis of Formulations: Dosing solutions had actual concentrations within 10% of their nominal concentration.

Mortality: A total of 27 drug-treated animals (23 males, 4 females) died during the study. Mortality was dose-dependent for both the main study and toxicokinetics groups (Table 3.2.2.3). The majority of the deaths occurred following the first 1.5 mg/kg/day dose. This led to dividing the high dose, with two half-doses administered approximately 1 to 2 hr apart. In most of the cases dead animals were replaced by spare animals. Even the replacement animals were subsequently found dead within the first 2 days of dosing. The incidence of mortality was consistently higher for males than for females with the exception of a single female in the low dose group, which was not related to treatment. This female died on study day 3 due to persistent diarrhea which was not present in any other animal on study. Animals that died typically exhibited blood around the nostrils and red-spotted lungs at necropsy. The cause of death was most likely pulmonary edema and/or hemorrhage due to reduced perfusion as a result of the vasoconstrictive action of terlipressin. A dramatic increase in peripheral vascular resistance, due to a rapid onset of

sudden and severe vasoconstriction, can result in acute heart failure. In the toxicokinetics groups, deaths occurred primarily in those animals bled at 5 min post dose. Thus, it was suggested that deaths in the toxicokinetics groups were due to a combination of the vasoconstrictive activity of terlipressin plus the stress of restraint and bleeding. However, the incidence of mortality in the toxicokinetics groups was not higher than in the main study groups. Histopathological examination was not done on any of these animals.

TABLE 3.2.2.3
28 DAY TOXICITY STUDY IN RATS: INCIDENCE OF MORTALITY

Daily Dose (mg/kg/day)	Group	Sex	Total incidence of mortality	Day of death (incidence of mortality)	Animal No.	Actual doses received (mg/kg)
Main toxicology study groups						
0	1	M	0/15			
		F	0/15			
0.15	2	M	0/15			
		F	1/15	Day 3 (1/15)	261	0.15 [a]
0.5	3	M	4/19	Day 0 (4/19)	304, 306, 311, 315	0.5
		F	0/15			
1.5	4	M	12/19 [b]	Day 0 (9/15)	402, 406, 408, 412, 414, 415, 416, 417, 418	1.5
				Day 1 (3/10) [b]	407 413 419	1.5, 0.75 1.5 1.5, 0.75
		F	2/17 [b]	Day 0 (1/15)	465	1.5
				Day 2 (1/15) [b]	454	1.5, 0.75, 0.75, 0.75
Toxicokinetic groups						
0.15	5	M	1/10 [b]	Day 0 (1/10)	502 [c]	0.15
		F	0/9			
0.5	6	M	2/11 [b]	Day 0 (2/11)	604, 606	0.5
		F	0/9			
1.5	7	M	4/13 [b]	Day 0 (4/13) [b]	701, 704, 706, 709	1.5
		F	1/10 [b]	Day 0 (1/10) [b]	755	1.5

a: Because of diarrhea on Days 1 and 2, Rat 261 received only a single (Day 0) dose; this animal was not replaced.
b: Includes replacement animals
c: The Time 0 bleed for TK analysis was taken 1 min before dosing, and Rat 502 died within 30 min of receiving the dose

Clinical Signs: Clinical signs were test substance-related and dose-dependent. They were noted only during the dosing period and were absent during the recovery period. The number of animals suffering from lethargy and pale skin color increased with increase in dose. Labored breathing, increased respiratory rate, immobility and loss of use of rear legs were noted in high dose animals. Most of the high dose animals exhibited foaming blood around the nostrils. These signs progressively decreased over several hours following dosing.

Body Weights: For males, a significant ($p < 0.05$) reduction in body weight gain relative to control was noted at all dose levels throughout the treatment and the recovery period (Fig. 3.2.2.1). No effect on body weight was noted for females at any dose level (Fig. 3.2.2.2).

Food Consumption: A statistically significant reduction in mean food consumption relative to control was noted for treated males and females at all dose levels during week

1. The consumption recovered and increased for some groups in subsequent weeks of the study.
Ophthalmoscopy: No significant changes
Hematology: A slight dose-dependent decrease (statistically significant for the high dose group) relative to control in hematological parameters for both males and females was noted. Only one high dose male survived until the day 42 necropsy and this male and the recovery group females showed no differences from control.

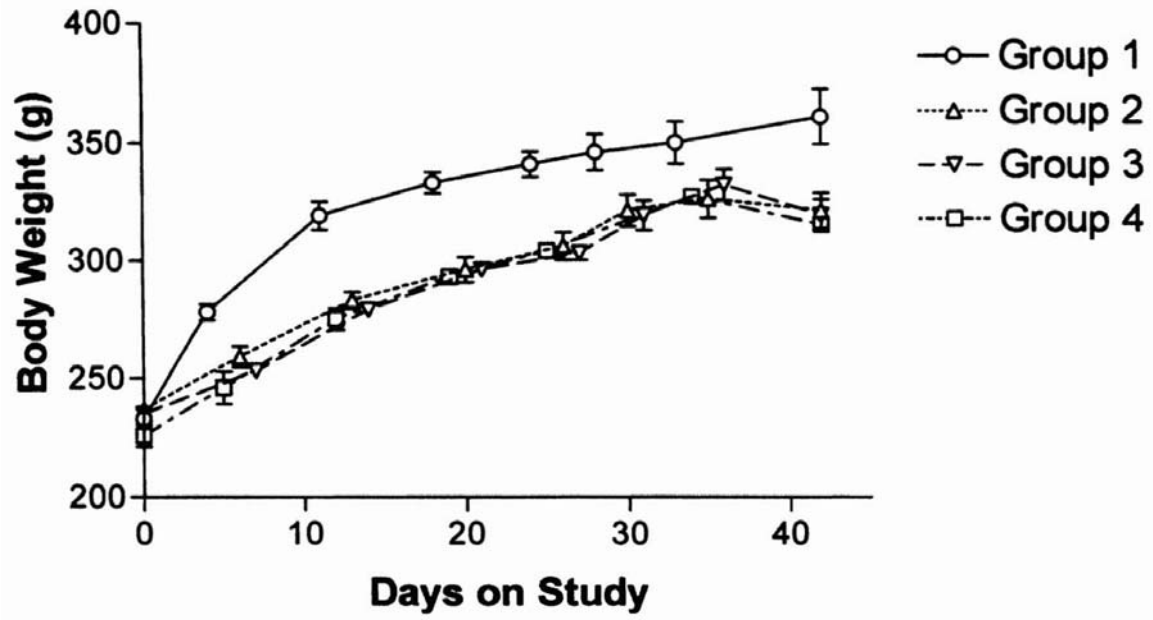

FIG. 3.2.2.1.: Group mean body weights for males. Error bars show ± SEM

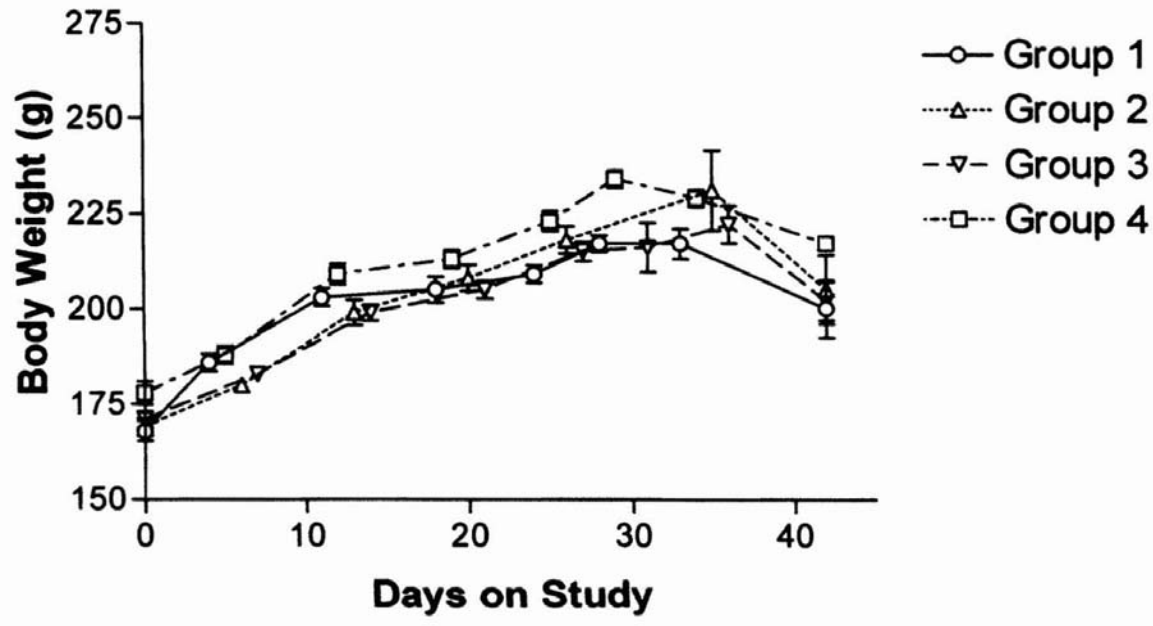

FIG. 3.2.2.2.: Group mean body weights for females. Error bars show ± SEM

Clinical Chemistry: Small but dose-dependent decreases ($p < 0.05$) relative to control in liver enzymes (AST, ALT, AP) for males at all doses were reported. The sponsor does not consider these changes to be toxicologically significant. There were no reportable significant differences from control in recovery groups.
Urinalysis: There were no significant changes.
Organ Weights: Small but significant ($p < 0.05$) and nondose-dependent decreases in mean kidney and testes weights (both absolute and relative to final body weight) relative to control were noted for males at all doses. Females showed small but statistically significant nondose-dependent increases in mean heart, liver and adrenal weights (both absolute and relative to final body weight) relative to control at all doses. None of these organs had any histopathological findings. Thymus weights (both absolute and relative to body weight) were reduced ($p < 0.05$) relative to control for females receiving 0.5 or more mg/kg/day group.
Gross Pathology: Many of the animals in the treated groups (including recovery group animals) had discolorations and/spotting on the kidneys and liver. Additionally, many of the animals receiving 0.15 or 0.5 mg/kg/day (but not 1.5 mg/kg/day) had enlarged adrenals (no difference from control in recovery group animals).
Histopathology: Significant histopathological findings considered related to treatment with terlipressin diacetate pentahydrate were noted in the kidney, testes, thymus, and injection sites (Table 3.2.2.4). Mild to moderate nephritis, probably ischemic in origin was noted in 5/6 males and 8/10 females at 1.5 mg/kg/day, and 1/9 males and 1/10 females at 0.5 mg/kg/day. These lesions consisted of multifocal tubular dilation in the cortex with some non-suppurative interstitial inflammation. Kidney findings were absent in the control group. In the testes, seminiferous tubular degeneration was mild to moderate in 5/10 mid dose males, and mild or severe in 4/6 high dose males. It was absent in the control and low dose groups. Trace to mild cortical lymphoid depletion of the thymus was observed in all treated and control groups and was considered by the sponsor to be an indication of stress. At the injection site, variable perivascular inflammation was noted sporadically in all treated but not control groups. In the recovery group animals, the lone surviving high dose male showed trace nephritis and moderate (severe in one mid dose male) seminiferous tubular degeneration. The thymus was normal and the injection site was free of inflammation in all recovery group animals.

TABLE 3.2.2.4
28 DAY TOXICITY STUDY IN RATS: TREATMENT-RELATED HISTOPATHOLOGICAL FINDINGS

	Control		0.15 mg/kg/d		0.5 mg/kg/d		1.5 mg/kg/d	
	M	F	M	F	M	F	M	F
No. of animals	15	15	15	15	19	15	19	17
No. examined[1]	10/5	10/4	8/5	10/5	9/4	10/4	6/1	10/5
Kidney, Chronic nephritis	0	0	1	0	1	1	5	8
Recovery gp	0	0	0	0	0	0	1	0
Testes, tubular degn	0		0		5		4	
Recovery gp	0		0		1		1	
Thymus, lymphoid depln	5	2	1	1	5	8	4	8
Recovery gp	0	0	0	0	0	0	0	0

[1]: Number of animals examined at the end of 28 day of dosing/ at the end of 2 week recovery period

Toxicokinetics: Deviating from the protocol, a limited number of samples per time point were studied due to deaths and difficulty in collecting blood due to the vasoconstrictive effect of the drug. Though data were not subjected to statistical analysis, some general conclusions are drawn from the study. Detectable plasma concentrations of both terlipressin and its metabolite lysine-vasopressin were achieved after intravenous administration of terlipressin diacetate pentahydrate. The plasma concentrations of these substances appeared to increase with an increase in dose administered. Both terlipressin and lysine-vasopressin are rapidly eliminated, with a half-life of 0.2 and 1.9 hr, respectively (Table 3.2.2.5). This confirms the rapid conversion of terlipressin to low but slightly more sustained concentrations of lysine-vasopressin. At 1.5 mg/kg/day, the observed exposure to terlipressin and lysine-vasopressin was in the order of 40- to 90-fold greater than that seen in humans receiving 1 mg terlipressin. Similarly, at 0.5 mg/kg/day and 0.15 mg/kg/day, the observed exposure to terlipressin and lysine-vasopressin was in the order of 17- and 6-fold, respectively, greater than that seen in humans receiving 1 mg terlipressin. There was no accumulation of terlipressin or lysine-vasopressin, as evidenced by concentrations below quantifiable limits at 0 and 2 hr post dose on dosing day 27. No gender differences in plasma concentration were noted.

TABLE 3.2.2.5
PHARMACOKINETIC PARAMETERS OF TERLIPRESSIN AND LYSINE-VASOPRESSIN ON DAY 27 IN RAT PLASMA

Mean (N=2)	Cmax, ng/ml	T1/2, hours	MRT, Hours	AUClast, ng x hr/ml	AUCinf ng x hr/ml
Terlipressin					
0.75 mg/kg*	5385	0.215	0.153	829.7	841.6
0.5 mg/kg	1078	0.09	0.175	246.4	252.1
0.15 mg/kg	352.1	NC	0.10	51.14	NC
Lysine-Vasopressin					
0.75 mg/kg*	75.1	1.85	2.69	53.5	175.1
0.5 mg/kg	21.5	0.46	0.731	16.0	21.0
0.15 mg/kg	9.25	NC	0.15	1.94	NC

Cmax-maximal plasma concentration
T1/2 elimination half-life for terlipressin, apparent half-life for lysine-vasopressin
MRT mean residence time
AUClast area under the plasma concentration time curve from time zero to last measurable timepoint.
AUCinf area under the plasma concentration time curve from time zero to infinity.
NC not calculable

* Total daily dose of 1.5 mg/kg/day administered as two split doses of 0.75 mg/kg/dose

3.2.3. A 28 Day Intravenous Toxicity Study in Dogs with a 14 Day Recovery

Key Study Findings: Terlipressin dosed animals displayed a dose-related increase in severity of clinical signs (lethargy, emesis, defecation). Histopathological examination of drug-treated (but not control) dogs revealed multifocal chronic nephritis, interstitial lymphocytic infiltration, and/or tubular dilation in the kidneys for both sexes at all doses. A NOAEL could not be determined.

Study No.: CB06-5089-D-TX
Location of Report: Module 4, Vol 8 of 14
Conducting Laboratory and Location: (b) (4)
Dates of Study: The animals were dosed on August 29; last necropsy was on October 17, 2006.
GLP Compliance: Yes
QA'd Report: Yes
Drug, Lot #: Terlipressin diacetate pentahydrate, #V125//165-111 supplied by (b) (4) Net peptide content was 82% and concentrations were expressed as anhydrous free base.
Formulation: Terlipressin diacetate pentahydrate was formulated in sterile saline for injection and prepared fresh daily. Dosing solutions had actual concentrations ranging from 87% to 90% of their nominal concentration.
Animals

Species/Strain: Purebred beagle dogs (*Canis lupus familiaris*)
#/Animals/Sex/Group: For control and high dose groups: 3 for treatment phase and 1 for recovery phase. For low and mid dose groups: 3 with no recovery phase. See Table 3.2.3.1 for details.
Age: 8-12 months old at initiation of dosing
Weight: Males: 6.55-12.20 kg, Females: 6.10-7.80 kg, at initiation of dosing
Husbandry: Animals were individually housed in steel cages. Food, 25 gm/kg, and water *ad libitum* were given throughout the study period.

Dosing

Dogs were dosed intravenously at 0, 0.031, 0.0625 or 0.125 mg/kg/dose twice daily for 28 consecutive days (day 0 through day 27). The dose and route of administration were selected by the sponsor for the contract laboratory based on a previous dose range-finding study. In that study, MTD was reached at 0.15 mg/kg/day, b.i.d. given for 7 days. This dose resulted in vomiting, defecation, panting, and unwilling to walk. Histopathologically, mild, multifocal renal tubular dilatation was seen. Due to severe clinical signs noted in the first hour of dosing in the dose range-finding study, animals in the 28 day study were dosed twice daily, about 6 hr apart, intravenously by a slow (5-10 sec) bolus (0.25 ml/kg) *via* the cephalic or saphenous vein. Control animals received the vehicle. On day 28, 3 males and 3 females from each group were sacrificed. A single male and female from control and high dose groups ('recovery' animals) were maintained untreated for an additional 14 days. These dogs were sacrificed on day 42.

TABLE 3.2.3.1
STUDY DESIGN

Group	Dose (mg/kg/dose, b.i.d., 28 days)	Animal Numbers (M/F)	
		Treatment Phase	Recovery Phase
1	0	101-103/151-153	104/154
2	0.031 (0.0625 mg/kg/day)	201-203/251-253	-
3	0.0625 (0.125 mg/kg/day)	301-303/351-353	-
4	0.125 (0.25 mg/kg/day)	401-403/451-453	404/454

Observations and Measurements

Clinical Signs: All animals were observed twice daily for clinical signs and mortality.
Body Weight: Recorded on first day of dosing, once weekly during the course of study, and at necropsy.
Food Consumption: Daily on weekdays during the course of study.
Ophthalmology: Conducted prior to study and at necropsy.
Hematology[1] and Clinical chemistry[2]: Blood samples were collected from all surviving animals prior to the start of dosing and at necropsy including recovery group.
Urinalysis[3]: Determined at necropsy.
ECG: ECGs were recorded from awake and unrestrained dogs prior to the start of dosing (day -7), prior to the treatment phase sacrifice (day 28, 3 hr after the last preceding dose) and prior to the recovery sacrifice.
Pathology: Animals were not fasted prior to terminal necropsy. Animals in the treated and recovery groups were euthanized on day 28 and day 42, respectively. No necropsy was done on surviving toxicokinetics group animals. No histopathology was done on animals that died during the study. Protocol specified organs were weighed and tissues collected for histopathological evaluation. Microscopic examination was performed on all tissues listed in Table 3.2.3.2 from all animals in the control, treatment and recovery groups.
Toxicokinetics: Blood samples for determination of levels of terlipressin and lysine vasopressin were collected from drug treated groups on study days 0 (1st dose) and 27 (28th dose) at 0 (prior to dosing), 5, 15 and 30 min, and 1, 2, 4, 6, 8 and 24 hr after dosing. The collection of blood was not successful after the 1st dose due to the vasoconstrictor effect of terlipressin and, thus, samples per time point varied from 1 to 4. Statistical analysis was not performed.

[1] erythrocytes, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocytes, white blood cell count, white blood cell differential, platelets, prothrombin time, activated partial thromboplastin time
[2] ALT, AST, AP, total bilirubin, total protein, albumin, globulins, A/G ratio, glucose, BUN, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol
[3] Color, volume, specific gravity, pH, microscopic examination of sediment, bilirubin, blood glucose, ketones, protein, urobilinogen, leukocytes

TABLE 3.2.3.2
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenal glands (paired)*	Mammary gland (inguinal)
Aorta (thoracic)	Ovaries (paired)*
Bone (sternum, femur)	Oviducts (paired)
Bone marrow (femur, sternum, b m smear)	Pancreas
Brain (cerebrum, cerebellum, mid-brain)*	Pituitary gland*
Cecum	Prostate*
Colon	Rectum
Duodenum	Salivary gland
Epididymis	Sciatic nerve
Esophagus	Seminal vesicles
Eyes w/optic nerve	Skeletal muscle
Gall bladder	Skin and subcutis (inguinal)
Harderian gland	Spinal cord – cervical, lumbar, thoracic
Heart*	Spleen*
Injection site, leg	Stomach
Ileum	Testes (paired)*
Jejunum	Thymus*
Kidneys (paired)*	Thyroid (incl. parathyroid)*
Lacrimal gland	Tongue
Liver (2 lobes)*	Trachea
Lungs with bronchi	Uterus/Cervix
Lymph nodes (mesenteric, inguinal)	Vagina
Macroscopic lesions	

*: Organ weight obtained

Results

Due to the small number of animals, statistical significance testing was not performed for any of the measured parameters.

Analysis of Formulations: Dosing solutions had actual concentrations within 10% of their nominal concentration.

Mortality: There were no deaths in the study.

Clinical Signs: Test substance-treated animals showed dose-dependent severity of signs. The first dose resulted in yellow, frothy vomiting; licking of lips and gums; delayed capillary refill; defecation (wet stools) and lethargy. These signs progressively decreased over 60 min, were less severe following second day dosing and were largely absent following subsequent doses and during the recovery period.

Body Weights: A decrease in body weight gain was noted for all dose groups relative to control. It was dose-dependent and larger for males (7, 14 and 20% lower than control at 0.0625, 0.125 and 0.25 mg/kg/day, respectively; Fig. 3.2.3.1) than females (5, 4 and 6% lower than control at 0.0625, 0.125 and 0.25 mg/kg/day, respectively; Fig. 3.2.3.2) on study day 28.

Food Consumption: Little variation among groups.

Ophthalmoscopy: No significant findings

ECG: No remarkable findings.

Hematology: A trend toward a dose-dependent decrease (relative to control) in hematological parameters for males.

Clinical Chemistry: Values for the treatment groups were within normal limits.

Urinalysis: No differences between control and treatment groups.

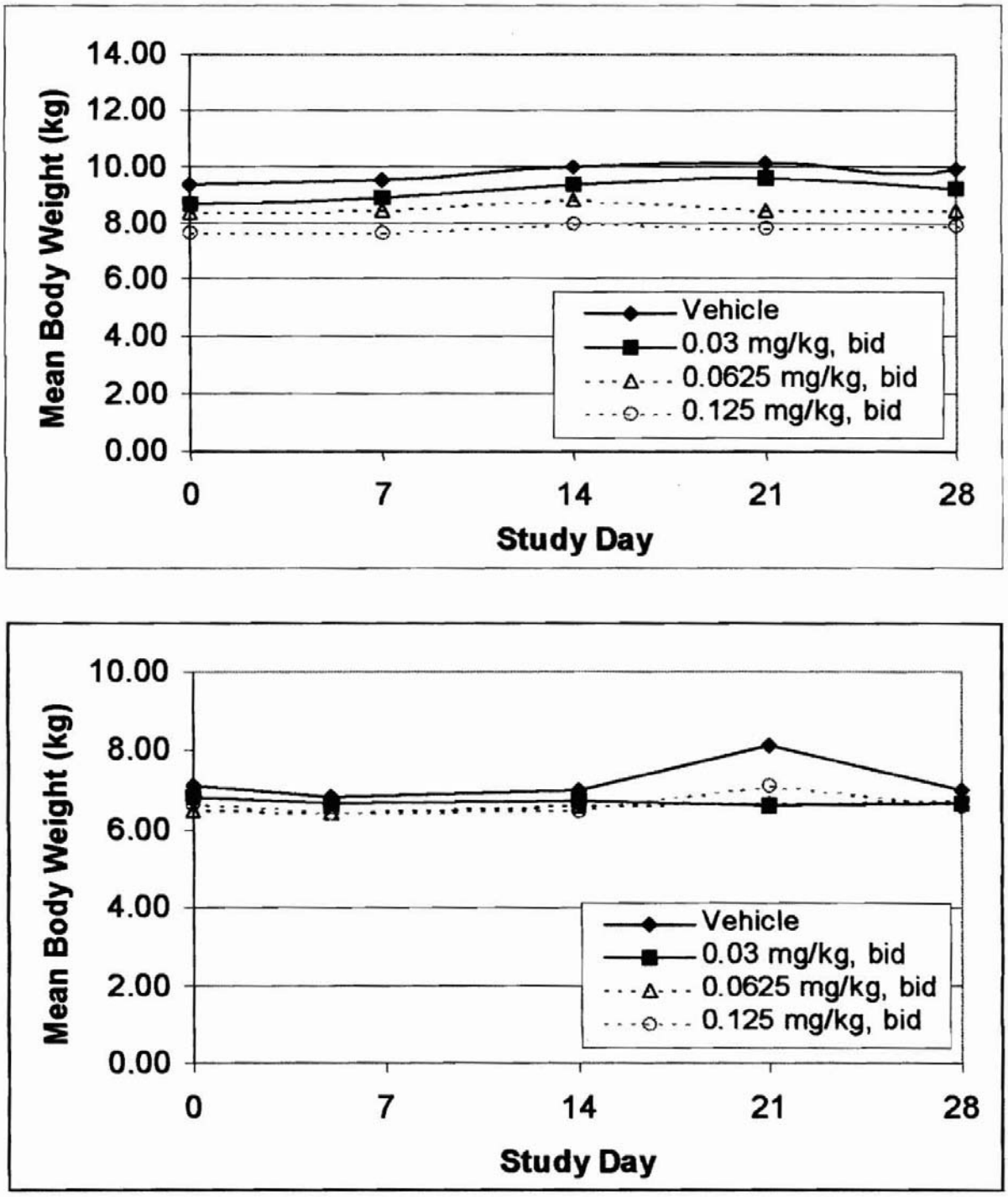

Fig. 3.2.3.1.: Mean body weights during treatment period. Males (upper panel) and females (lower panel)

Organ weights: A dose-dependent decrease in mean absolute kidney weight was noted for males at all doses (11, 13 and 19% at 0.0625, 0.125 and 0.25 mg/kg/day, respectively) relative to control. A non dose-dependent increase in absolute and relative (to final body weight) spleen weight was noted for females relative to control.
Gross Pathology: No treatment-related findings

Histopathology: Terlipressin, in a dose-related manner, induced mild multifocal chronic cortical nephritis (0/6, 1/6, 2/6 and 3/6 dogs, respectively, at 0, 0.0625, 0.125 and 0.25 mg/kg/day), interstitial lymphocytic infiltration (0/6, 1/6, 0/6 and 3/6 dogs, respectively, at 0, 0.0625, 0.125 and 0.25 mg/kg/day), and/or tubular dilation (one high dose female). In the recovery group animals, trace nephritis was still noted in the male but not in the female (Table 3.2.3.3). Perivascular inflammation, hemorrhage and edema at the injection sites were noted in both treated (non-dose-dependent) and control groups and were absent after the recovery period. Mild pulmonary inflammation was found in 14/18 terlipressin-dosed animals (non-dose-dependent) and one of six control dogs.

TABLE 3.2.3.3
28 DAY TOXICITY STUDY IN DOGS: TREATMENT-RELATED HISTOPATHOLOGICAL FINDINGS IN KIDNEYS

	Control		0.03 mg/kg/d		0.0625 mg/kg/d		0.125 mg/kg/d	
	M	F	M	F	M	F	M	F
No. of animals[1]	3/1	3/1	3	3	3	3	3/1	3/1
chronic cortical nephritis	0	0	1	0	0	2	2	1
Recovery gp	0	0					1	0
tubular dilatation	0		0	0	0	0	0	1
Recovery gp	0						0	0
infiltration, lymphocytic	0	0	0	1	0	0	1	2
Recovery gp							0	0
mineralization	0	0	0	1	1	1	1	1
Recovery gp	0	0					0	0

[1]: Number of animals at the start of study and number of animals examined at the end of 28 day of dosing/ at the end of 2 week recovery period are the same.

Toxicokinetics: Detectable plasma concentrations of both terlipressin (Table 3.2.3.4) and its metabolite lysine-vasopressin (Table 3.2.3.5) were achieved in all animals and at all dose levels after intravenous administration of terlipressin diacetate pentahydrate. The plasma concentrations of these substances did not show a consistent increase with increasing dose on either study day 0 or study day 27. There was a poor correlation between Cmax and AUC values. Terlipressin was detectable for longer periods (for up to 8 hrs) after chronic administration as a consequence of the BID regimen. Thus, there were higher levels of terlipressin on day 27 than on day 0. Both terlipressin and lysine-vasopressin were rapidly eliminated, especially after the first dose. On day 0, terlipressin was not detectable in plasma after 30 min. An elimination half-life was not calculable. No consistent gender difference in plasma concentration was noted.

TABLE 3.2.3.4
PHARMACOKINETIC PARAMETERS OF TERLIPRESSIN IN DOG PLASMA

Table 2: Mean Pharmacokinetic Parameters For Terlipressin Day 0 Derived from Mean Plasma Concentration Time Profiles

	Cmax ng/ml	Tmax hours	AUC0-8 hours	AUC0-24 ng x hr/ml	T1/2 hours
MALES					
Treatment A (n=3) 0.031 mg/kg/dose	81.4	0.083	12.26	12.27	NC
Treatment B (n=3) 0.0625 mg/kg/dose	187	0.083	31.26	31.26	NC
Treatment C (n=4) 0.125 mg/kg/dose	395	0.083	68.64	68.64	NC
FEMALES					
Treatment A (n=3) 0.031 mg/kg/dose	30.0	0.083	3.75	1747	NC
Treatment B (n=3) 0.0625 mg/kg/dose	41.1	0.083	5.13	513.5	NC
Treatment C (n=4) 0.125 mg/kg/dose	246.8	0.083	44.25	342.9	NC

Cmax-maximal plasma concentration
Tmax= time of maximal plasma concentration
T1/2 elimination half-life
AUC under the plasma concentration time curve from time specified endpoint
NC not calculable

Table 3: Mean Pharmacokinetic Parameters For Terlipressin On Day 27 Derived from Mean Plasma Concentration Time Profiles

	Cmax ng/ml	Tmax hours	AUC0-8 hours	AUC0-24 ng x hr/ml	T1/2 hours
MALES					
Treatment A (n=3) 0.031 mg/kg/dose	72.3	0.083	289.2	289.2	NC
Treatment B (n=3) 0.0625 mg/kg/dose	428.9	0.083	241.5	241.5	NC
Treatment C (n=4) 0.125 mg/kg/dose	392	0.083	267.7	267.7	NC
FEMALES					
Treatment A (n=3) 0.031 mg/kg/dose	131.6	0.083	346.5	2051.6	NC
Treatment B (n=3) 0.0625 mg/kg/dose	198.4	0.083	673.7	1363.1	NC
Treatment C (n=4) 0.125 mg/kg/dose	761.3	0.083	1048.2	1893.2	NC

Cmax-maximal plasma concentration
Tmax= time of maximal plasma concentration
T1/2 elimination half-life
AUC under the plasma concentration time curve from time specified endpoint
NC not calculable

TABLE 3.2.2.5
PHARMACOKINETIC PARAMETERS OF LYSINE-VASOPRESSIN IN DOG PLASMA

Table 4: Mean Pharmacokinetic Parameters For Lysine-Vasopressin On Day 0 Derived from Mean Plasma Concentration Time Profiles

	Cmax ng/ml	Tmax hours	AUC0-8 hours	AUC0-24 ng x hr/ml	T1/2 hours
MALES					
Treatment A (n=3) 0.031 mg/kg/dose	2.16	0.5	1.15	1.15	NC
Treatment B (n=3) 0.0625 mg/kg/dose	5.69	0.5	5.48	5.48	NC
Treatment C (n=4) 0.125 mg/kg/dose	10.21	0.25	9.14	9.14	NC
FEMALES					
Treatment A (n=3) 0.031 mg/kg/dose	0.74	0.5	0.42	0.42	NC
Treatment B (n=3) 0.0625 mg/kg/dose	2.44	0.25	0.67	0.67	NC
Treatment C (n=4) 0.125 mg/kg/dose	7.66	0.5	6.27	6.27	

Cmax-maximal plasma concentration
Tmax= time of maximal plasma concentration
T1/2 elimination half-life
AUC under the plasma concentration time curve from time specified endpoint
NC not calculable

Table 5: Mean Pharmacokinetic Parameters For Lysine-Vasopressin On Day 27 Derived from Mean Plasma Concentration Time Profiles

	Cmax ng/ml	Tmax hours	AUC0-8 hours	AUC0-24 ng x hr/ml	T1/2 hours
MALES					
Treatment A (n=3) 0.031 mg/kg/dose	1.04	0.25	0.60	0.60	35.9
Treatment B (n=3) 0.0625 mg/kg/dose	1.76	0.5	1.60	1.60	0.38
Treatment C (n=4) 0.125 mg/kg/dose	8.99	0.5	17.3	17.3	1.76
FEMALES					
Treatment A (n=3) 0.031 mg/kg/dose	2.80	0.25	2.37	2.37	0.47
Treatment B (n=3) 0.0625 mg/kg/dose	1.89	0.5	2.22	2.22	2.27
Treatment C (n=4) 0.125 mg/kg/dose	12.89	0.5	17.95	17.95	0.6

Cmax-maximal plasma concentration
Tmax= time of maximal plasma concentration
T1/2 elimination half-life
AUC under the plasma concentration time curve from time specified endpoint
NC not calculable

3.3. Genetic Toxicology

3.3.1. Ames Assay. *In Vitro* Bacterial Test of Terlipressin

Key Findings: Terlipressin diacetate pentahydrate was reproducibly negative in all tester strains both with and without metabolic activation.

Study No: AB25XV.503 (b) (4)
Location of Report: Module 4, Vol 11 of 14
Conducting Laboratory and Location: (b) (4)
Dates of Study: Initiated on 21 March and terminated on 30 May 2006.
GLP Compliance: Yes
QA'd Report: Yes

Methods

Four *Salmonella typhimurium* strains and one *Escherichia coli* strain were used, with and without metabolic activation. The *S. typhimurium* strains were, TA98, TA100, TA1535, and TA1537; the *E. coli* strain, WP2*uvr*A. Terlipressin diacetate pentahydrate (batch #V125//165-111 supplied by (b) (4)) was dissolved in sterile distilled water. Concentrations were expressed as anhydrous free base. A dose range-finding study to determine the highest dose level of terlipressin diacetate pentahydrate for the reverse mutation study and to provide a preliminary mutagenicity evaluation was carried out with all five tester strains. Terlipressin diacetate pentahydrate was tested at doses of 1.5 to 5000 µg/plate (2 plates/dose) with and without metabolic activation. Vehicle and positive controls were also included. No toxicity was observed. Thus, the main study was carried out using 5000 µg/plate as the highest dose. The confirmatory experiment was performed using 5 doses of the test substance (50, 150, 500, 1500 and 5000 µg/plate), a negative (water) and a positive control. For each test dose, 3 plates were used. The test system was exposed to the test substance *via* the plate incorporation method. Statistical analyses were not carried out.

Basis of dose selection: Cytotoxicity

Metabolic activation system: S9 homogenate (liver microsomal enzymes) prepared from the liver of a male Sprague-Dawley rat given Aroclor 1254 (500 mg/kg, i.p.) 5 days before sacrifice.

Controls

Negative control: Sterile distilled water (one group)

Positive controls: Each tester strain was treated with an appropriate positive control substance (Table 3.3.1.1).

Criteria for a valid study: The assay is considered acceptable if the solvent control mutant frequency for all tester strains are within the laboratory's normal control range for spontaneous mutant frequency and the positive controls induce increases in the mutation frequency which is at least a 3-fold increase in the number of revertants over the mean value of the respective vehicle control.

Criteria for a positive result: For test substance to be considered positive, it had to produce a dose-dependent effect on mean revertants/plate of at least one tester strain, reaching 2 or more times the corresponding negative control count for strains TA98,

TA100 and *E. coli* WP2uvrA; 3.0 times the corresponding negative control count for strains TA1535 and TA1537.

TABLE 3.3.1.1
BACTERIAL REVERSE MUTATION ASSAY. POSITIVE CONTROLS

Strain	Direct method		Metabolic activation method	
	Substance	Conc. µg/plate	Substance	Conc. µg/plate
TA98	2-Nitrofluorene	1.0	2-aminoanthracene	1.0
TA100	Sodium azide	1.0	2-aminoanthracene	1.0
TA1535	Sodium azide	1.0	2-aminoanthracene	1.0
TA1537	9-Aminoacridine	75.0	2-aminoanthracene	1.0
WP2uvrA	Methyl methanesulfonate	1,000	2-aminoanthracene	10.0

Results

In both the initial dose range-finding and the confirmatory mutagenicity experiments performed with and without metabolic activation, treatment of strains TA98, TA100, TA1535, TA1537, and WP2uvrA with terlipressin diacetate pentahydrate did not lead to an increase in the incidence of histidine- or tryptophan-prototrophic mutants in comparison with the corresponding negative controls (Table 3.3.1.2). Neither precipitate nor reduction in the growth of the background lawn occurred with any of the strains at all concentrations studied. The positive control compounds induced reverse mutations in each strain, with revertant colony counts ranging from 4 to 84 times corresponding negative control count. Based on these results it is concluded that terlipressin diacetate pentahydrate did not induce gene mutations in bacteria under the conditions of the study.

TABLE 3.3.1.2
SUMMARY OF THE BACTERIAL REVERSE MUTATION ASSAY

Average Revertants Per Plate ± Standard Deviation

Liver Microsomes: None

Dose (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
Vehicle	13 ± 2	133 ± 4	31 ± 1	8 ± 4	28 ± 4
50	15 ± 3	125 ± 17	39 ± 6	9 ± 1	26 ± 1
150	17 ± 6	122 ± 7	40 ± 6	5 ± 1	32 ± 5
500	15 ± 2	123 ± 2	37 ± 3	6 ± 2	26 ± 3
1500	17 ± 5	135 ± 5	43 ± 4	5 ± 3	26 ± 4
5000	16 ± 3	126 ± 15	27 ± 4	6 ± 3	30 ± 3
Positive	169 ± 29	553 ± 59	394 ± 26	675 ± 235	136 ± 22

Liver Microsomes: Rat liver S9

Dose (µg/plate)	TA98	TA100[a]	TA1535	TA1537	WP2 uvrA
Vehicle	26 ± 6	97 ± 7	12 ± 4	8 ± 3	26 ± 3
50	23 ± 2	121 ± 5	12 ± 5	10 ± 3	23 ± 4
150	24 ± 6	114 ± 16	12 ± 3	9 ± 1	27 ± 5
500	26 ± 5	93 ± 3	16 ± 4	8 ± 1	21 ± 4
1500	21 ± 2	120 ± 15	14 ± 1	8 ± 2	26 ± 5
5000	19 ± 3	95 ± 14	10 ± 2	10 ± 4	24 ± 3
Positive	391 ± 85	480 ± 54	92 ± 7	66 ± 13	348 ± 6

Vehicle = Vehicle Control
Positive = Positive Control (50 µL plating aliquot)
Plating aliquot: 100 µL
a=Results from Experiment B4

3.3.2. *In Vitro* Mammalian Chromosome Aberration Test of Terlipressin

Key Findings: Terlipressin diacetate pentahydrate did not show any clastogenic potential in the chromosomal aberration test with Chinese hamster ovary cells both with and without metabolic activation.

Study No: AB25XV.331 (b) (4)
Location of Report: Module 4, Vol 11 of 14
Conducting Laboratory and Location: (b) (4)
Dates of Study: Initiated on 21 March and terminated on 30 May 2006.
GLP Compliance: Yes
QA'd Report: Yes

Methods

The clastogenic potential of terlipressin diacetate pentahydrate was evaluated in Chinese hamster ovary (CHO) cells in both the absence and presence of metabolic activation. The metabolic activation system was S9, prepared from the liver of a male Sprague-Dawley rat given Aroclor 1254 (500 mg/kg, i.p.) 5 days before sacrifice. An S-9 mix was prepared with cofactors immediately prior to use. Terlipressin diacetate pentahydrate (batch #V125//165-111 supplied by (b) (4)) was dissolved in sterile distilled water. Concentrations were expressed as anhydrous free base. Tests conducted without the S9 mixture are considered to have been conducted by the "direct method." Two kinds of experiments were conducted: a preliminary toxicity assay and a chromosome aberration assay. The preliminary toxicity assay was performed for the purpose of selecting dose levels for the chromosome aberration assay. In the dose range-finding assay, the cells were exposed to a medium containing the test substance (concentrations ranging from 50 to 5000 µg/ml) for 4 hr in the absence and presence of S9 mix and continuously for 20 hr in the absence of S9 mix at 37°C. At the end of the 4 hr exposure period, the treatment medium was removed, the cells washed and the medium replaced with a fresh medium, excluding the test substance and S9 mixture, and continued in culture for an additional 16 hours, for a total of 20 hr from the initiation of treatment. At 20 hr after the initiation of treatment, the cells were harvested and counted using a Coulter counter. The cell counts and percent viability were used to determine cell growth inhibition relative to the solvent control.

Dose levels for the chromosome aberration assay were selected from the preliminary toxicity assay. The experimental design is shown in the following Table (3.3.2.1). Duplicate cultures of CHO cells were exposed to test substance, positive and negative controls at 37°C. The cells were exposed to a medium containing test substance for 4 hr in the presence and absence of S9 mix or continuously for 20 hr in the absence of S9 mix. In the case of the 4 hr exposure, the treatment medium was removed; the cells washed and the medium replaced with a fresh medium excluding the test substance and S9 mix, and continued in culture for an additional 16 hours. Two hours prior to harvesting, the cultures were treated with colcemide (final concentration 0.1 µg/ml) to arrest cells in metaphase. At 20 hr after the initiation of treatment, the cells were harvested. A minimum of 200 well spread metaphases from vehicle control and treated cultures (100

metaphases per replicate culture) were scored for chromatid-type and chromosome-type aberrations. Cyclophosphamide (+S9) and mitomycin-C (-S9) were used as positive control cultures.
A concurrent toxicity test was conducted in both the absence and presence of the metabolic activation system.

TABLE 3.3.2.1
EXPERIMENTAL DESIGN

	Preliminary Tox assay			Chromosome aberration assay		
Expt. #	1	2	3	1	2	3
Metabolic activation	-	-	+	-	-	+
Treatment with terlipressin (h)	4	20	4	4	20	4
Recovery after treatment (h)	16	0	16	16	0	16
Concentration (µg/ml) used	50 to 5000	50 to 5000	50 to 5000	625 1250 2500 5000	625 1250 2500 5000	625 1250 2500 5000
Toxicity, % (cell growth inhibition), at the highest dose		31	17	12	4	8
Mitotic index reduction, %*				8	4	5

*: relative to solvent control a the highest dose (5000 µg/ml) evaluated for chromosome aberrations

Since substantial toxicity (at least 50% cell growth inhibition relative to the solvent control) was not observed in the preliminary toxicity assay, the highest dose selected for the analysis of chromosome aberrations was not different from that used earlier. The slides were examined for the following structural aberrations.

Chromatid-type aberrations that include chromatid and isochromatid breaks and exchange figures such as quadriradials, triradials, and complex rearrangements.
Chromosome-type aberrations that include chromosome breaks and exchange figures such as dicentrics and rings.
Fragments (chromatid or acentric) observed in the absence of any exchange figure were scored as a break (chromatid or chromosome).
Pulverized chromosome(s), pulverized cells and severely damaged cells were also recorded.
Chromatid and isochromatid gaps were recorded but not included in the analysis.
Incidence of polyploid and endoreduplicated were also scored.

The evaluated numbers of specific aberrations were subjected to statistical analysis. The test substance is considered to have tested positive if the percentage of cells with aberrations is increased in a dose-related manner with per cent aberrant cells at one or more concentrations being significantly greater than concurrent control and above the range of historical solvent controls.

Results

Terlipressin diacetate pentahydrate did not produce appreciable toxicity at any dose level (±S9 mix). Toxicity never exceeded 12% (cell growth inhibition) relative to solvent control at the highest concentration used (5000 µg/ml). Mitotic index at the highest dose

level was 8% reduced relative to solvent control. The percentage of cells with structural or numerical chromosomal aberrations at all concentrations in the chromosome aberration assays performed with or without metabolic activation was not significantly increased relative to solvent control ($p > 0.05$, Table 3.3.2.2). The percentage of structurally damaged cells in cultures treated with the positive controls, mitomycin-C and cyclophosphamide, was significantly greater than control.

It is concluded that terlipressin diacetate pentahydrate does not have any clastogenic potential under the conditions of this chromosomal aberration test.

TABLE 3.3.2.2
CYTOGENETIC ANALYSIS OF CHO CELLS TREATED WITH TERLIPRESSIN DIACETATE PENTAHYDRATE IN THE ABSENCE AND PRESENCE OF METABOLIC ACTIVATION

Treatment µg/mL	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored		Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations	
				Numerical	Structural			Numerical (%)	Structural (%)
Water	-S9	4	10.2	200	200	0.005	±0.071	5.5	0.5
MPS-178									
1250	-S9	4	10.1	200	200	0.005	±0.071	3.5	0.5
2500	-S9	4	10.1	200	200	0.005	±0.071	4.0	0.5
5000	-S9	4	9.4	200	200	0.005	±0.071	4.0	0.5
MMC, 0.2	-S9	4	5.5	200	100	0.200	±0.471	3.5	17.0**
Water	+S9	4	11.2	200	200	0.000	±0.000	2.5	0.0
MPS-178									
1250	+S9	4	10.6	200	200	0.005	±0.071	5.0	0.5
2500	+S9	4	10.5	200	200	0.005	±0.071	5.0	0.5
5000	+S9	4	10.6	200	200	0.005	±0.071	5.0	0.5
CP, 10	+S9	4	3.9	200	50	0.460	±0.613	2.5	40.0**
Water	-S9	20	9.4	200	200	0.005	±0.071	3.5	0.5
MPS-178									
1250	-S9	20	9.6	200	200	0.005	±0.071	3.0	0.5
2500	-S9	20	9.6	200	200	0.005	±0.071	3.5	0.5
5000	-S9	20	9.0	200	200	0.010	±0.100	3.5	1.0
MMC, 0.1	-S9	20	4.4	200	100	0.190	±0.443	5.0	17.0**

Treatment: Cells from all treatment conditions were harvested 20 hours after the initiation of the treatments.
Aberrations per Cell: Severely damaged cells were counted as 10 aberrations.
Percent Aberrant Cells: *, $p \leq 0.05$; **, $p \leq 0.01$; using Fisher's exact test.
MPS-178: Terlipressin diacetate pentahydrate

3.3.3. *In vivo* Micronucleus Assay in Mice with Terlipressin

Key Findings: Terlipressin tested negative for inducing micronuclei in mouse bone marrow.

Study No: AB25XV.123 (b) (4)
Location of Report: Module 4, Vol 11 of 14
Conducting Laboratory and Location: (b) (4)
Dates of Study: Initiated on March 15 and terminated on April 13, 2006.
GLP Compliance: Yes
QA'd Report: yes

Methods

Prior to the main study, the maximum tolerated dose (MTD) of the test substance was determined. Six to 8 week old male and female mice (b) (4) weighing 28.3 to 34.20 gm, and 22.1 to 25.4 gm, respectively, were randomly assigned to 5 groups of 5 males and 5 females each. Terlipressin diacetate pentahydrate (lot #V125/165-111, 98.4% pure) was dissolved in 0.9% sodium chloride for injection and administered by a single bolus intravenous injection (10 ml/kg) into the lateral tail vein, initially at 20 mg/kg. Since mortality was not observed, additional animals were dosed with 500 or 1000 mg/kg and later back titrated with 600 or 750 mg/kg (n=5/sex/dose level). All animals were observed for 3 days for clinical signs of toxicity. Body weights were recorded before dose administration and 1 and 3 days post dose. Mortality was noted for 5/5 males and 5/5 females at 750 or more mg/kg; 2/5 males and 1/5 females at 600 mg/kg; and 1/5 males at 500 mg/kg. Lethargy was noted for all males and females at 20 or more mg/kg. Piloerection was observed for all males receiving 500 or more mg/kg. Hyperactivity, vocalization and excessive grooming were noted for all animals receiving 500 or more mg/kg. Convulsions were seen in all animals receiving 750 or more mg/kg. Based on these results, the MTD was estimated to be 500 mg/kg and was set as the highest dose for the definitive micronucleus study.

In the definitive study, terlipressin diacetate pentahydrate was administered once by IV injection at a dose of 125, 250 or 500 mg/kg to mice (n=5/sex/dose except for the high dose group, which was 15/sex). A negative control group (n=10/sex) was treated with the vehicle, and a positive control group (n = 5/sex) was treated with cyclophosphamide (50 mg/kg, i.v.). At the time of dose administration, the mice were approximately 6 to 8 weeks old; males weighed 26.8 to 31.10 gm and females weighed 20.0 to 24.3 gm. Mice were weighed before treatment and were observed after drug administration and throughout the study for clinical signs of toxicity. Animals from the high dose and the negative control groups were sacrificed 24 and 48 hr after administration (5/sex/harvest time). There was only one harvest (24 hr) for the other groups (5/sex) (Table 3.3.3.1). Bone marrow was harvested from the shafts of both femurs with fetal bovine serum. Bone marrow cells, polychromatic erythrocytes (PCEs) and normochromatic erythrocytes (NCEs) were analyzed for the presence of micronuclei. The ratio of PCE to NCE was determined and 2000 PCEs per mouse were scored for micronuclei. The incidence of micronucleated PCEs/2000PCEs for each mouse and per 10,000 PCEs for each treatment group was determined.

TABLE 3.3.3.1
EXPERIMENTAL DESIGN FOR DEFINITIVE STUDY

Treatment (10 mL/kg)	Number of Mice/Sex Dosed	Number of Mice/Sex Used for Bone Marrow Collection After Dose Administration	
		24 hr	48 hr
Vehicle Control: Saline	10	5	5
Test Article: Terlipressin Diacetate Pentahydrate			
Low dose (125 mg/kg)	5	5	0
Mid dose (250 mg/kg)	5	5	0
High dose (500 mg/kg)	15*	5	5
Positive Control: CP (50 mg/kg)	5	5	0

*Including 5 replacement mice per sex to ensure the availability of five mice for micronucleus analysis

The assay is considered valid provided the (a) incidence of micronucleated immature erythrocytes does not exceed 5/1000 PCE (0.5%) in the vehicle control group, and (b) the positive control induces a statistically significant increase in the incidence of micronucleated immature erythrocytes relative to the vehicle control group. The test is considered positive (a) if there is a dose-related increase in micronucleated PCEs, and (b) a statistically significant increase in the incidence at one or more dose levels relative to the vehicle control group.

Results

All concentrations were homogenous and stable at room temperature. The achieved concentrations were within 10% of target.

In the definitive study, a male receiving 500 mg/kg and assigned to the 48 hr harvest was found dead. Actual time of death and the cause of death are not given. No necropsy data. This animal was replaced with a male from the replacement group. Hyperactivity, vocalization and excessive grooming were noted for all males and females in all treatment groups. Piloerection and lethargy were observed in all males, respectively, at 250 or more mg/kg and at 500 mg/kg (Table 3.3.3.2).

TABLE 3.3.3.2
DEFINITIVE MICRONUCLEUS STUDY
CLINICAL SIGNS FOLLOWING IV DOSE OF TERLIPRESSIN IN MICE

		Number of Animals With Observed Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
Treatment (10 mL/kg)	**Observation**	**Males**	**Females**	**Males**	**Females**
Saline	Normal	10/10	10/10	0/10	0/10
Terlipressin (b) (4) (b) (4) 125 mg/kg	Hyperactivity	5/5	5/5	0/5	0/5
	Vocalization	5/5	5/5		
	Excessive grooming	5/5	5/5		
250 mg/kg	Piloerection	5/5	0/5	0/5	0/5
	Hyperactivity	5/5	5/5		
	Vocalization	5/5	5/5		
	Excessive grooming	5/5	5/5		
500 mg/kg	Lethargy	15/15	0/15	1/15	0/15
	Piloerection	15/15	0/15		
	Hyperactivity	15/15	15/15		
	Vocalization	15/15	15/15		
	Excessive grooming	15/15	15/15		
Cyclophosphamide 50 mg/kg	Normal	5/5	5/5	0/5	0/5

Dose-dependent reductions in the ratio of PCEs to total erythrocytes relative to the vehicle control groups, up to 17%, were observed for males. However, there was no dose-response for females (Table 3.3.3.3). Thus, the sponsor concludes that terlipressin does not inhibit erythropoiesis significantly. The number of micronucleated PCEs per 10,000 PCEs in test substance treated groups was not significantly different from the respective vehicle control in either male or female mice, regardless of dose level or bone marrow collection time.

The group mean frequencies of immature erythrocytes and micronucleated immature erythrocytes for the vehicle control were consistent with historical negative control data. The positive control, cyclophosphamide, induced a large and statistically significant increase in the frequency of micronucleated immature erythrocytes relative to concurrent control (Table 3.3.3.3). It is concluded that terlipressin diacetate pentahydrate tested negative in the mouse bone marrow micronucleus assay up to a dose of 500 mg/kg.

TABLE 3.3.3.3
MICRONUCLEUS TEST ON MOUSE BONE MARROW CELLS. SUMMARY DATA

Treatment (10 mL/kg)	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes Number/1000 PCEs (Mean +/- SD)	Micronucleated Polychromatic Erythrocytes Number/PCEs Scored[1]
Saline	M	24	5	0.532 ± 0.04	---	0.1 ± 0.22	1 / 10000
	F	24	5	0.452 ± 0.02	---	0.2 ± 0.27	2 / 10000
Terlipressin (b) (4)							
125 mg/kg	M	24	5	0.466 ± 0.07	-12	0.3 ± 0.27	3 / 10000
	F	24	5	0.397 ± 0.06	-12	0.1 ± 0.22	1 / 10000
250 mg/kg	M	24	5	0.448 ± 0.06	-16	0.0 ± 0.00	0 / 10000
	F	24	5	0.459 ± 0.06	2	0.2 ± 0.27	2 / 10000
500 mg/kg	M	24	5	0.440 ± 0.03	-17	0.1 ± 0.22	1 / 10000
	F	24	5	0.414 ± 0.11	-8	0.2 ± 0.27	2 / 10000
Cyclophosphamide							
50 mg/kg	M	24	5	0.351 ± 0.05	-34	10.3 ± 0.84	*103 / 10000
	F	24	5	0.362 ± 0.09	-20	10.7 ± 1.92	*107 / 10000
Saline	M	48	5	0.493 ± 0.02	---	0.0 ± 0.00	0 / 10000
	F	48	5	0.438 ± 0.05	---	0.2 ± 0.27	2 / 10000
Terlipressin (b) (4)							
500 mg/kg	M	48	5	0.472 ± 0.08	-4	0.1 ± 0.22	1 / 10000
	F	48	5	0.535 ± 0.07	22	0.2 ± 0.27	2 / 10000

[1]*Statistically significant, $p \leq 0.05$ (Kastenbaum-Bowman Tables)

4.0. OVERALL SUMMARY AND EVALUATION

Terlipressin is a synthetic 12 amino acid analog of the endogenous arginine vasopressin (AVP). It differs from AVP by the substitution of 'lysine' for 'arginine' at the 8th position of the endogenous molecule and the addition of three 'glycyl' residues at the amino terminus. The systemic vasoconstrictor effects of terlipressin are mediated through vascular vasopressin V_1 receptors (V_1R). It is a prodrug for lysine vasopressin but also has pharmacological activity of its own, albeit of much lower potency than lysine vasopressin. Compared to other VP analogues (including lysine vasopressin) terlipressin has a prolonged biological half-life (2-6 hr), which allows its administration as an i.v. bolus instead of a continuous i.v. infusion. The initial plasma concentration of terlipressin is about 100-fold higher than the peak concentration of lysine vasopressin. Additionally, terlipressin has been reported to induce a lower incidence of renal ischemic side effects than other VP analogues.

This new drug application from Orphan Therapeutics, LLC is for the use of terlipressin (Lucassin®) in the treatment of patients with hepatorenal syndrome type 1. The disease is a rare, functional renal failure in patients with end-stage liver disease that has a poor prognosis with >80% mortality within 3 months. The rationale for administering VP analogues (AVP, ornipressin, lypressin, terlipressin) is to counteract the extreme splanchnic arterial vasodilation in patients with cirrhosis and HRS. The vasoconstriction of the splanchnic circulation induced by VP analogues reduces portal venous blood flow, lowers portal pressure and contributes toward an increase in effective arterial blood volume which in turn improves circulatory function. This leads to a suppression of the activity of vasoconstrictor systems such as the sympathetic nervous system (that on activation releases both NE and neuropeptide Y) and the RAAS. Furthermore, stimulation of V_1R on the efferent (but not afferent) arterioles increases renal perfusion pressure and GFR. Since these agents also cause systemic vasoconstriction, ischemic side effects (cerebral and myocardial ischemia) are common.

The sponsor has not conducted any pharmacodynamic studies on terlipressin. Since terlipressin is given by direct intravenous injection, an *in vitro* study of red cell fragility was conducted. Terlipressin had no significant effect on red cell fragility and did not produce hemolysis when tested *in vitro* with human blood at concentrations up to 170 ng/ml. (Cmax at 2 mg QID is 138 ng/ml.) *In vitro* studies have demonstrated that terlipressin does not inhibit or induce the activity of the cytochrome P450 isoenzymes studied.

Toxicology

Acute Toxicity

Single dose intravenous toxicity studies were conducted with terlipressin diacetate pentahydrate in mice and rats. In mice, a single dose of 500 mg/kg was considered by the sponsor to be the maximum tolerated dose based on mortality and clinical signs. However, at this dose, there were clinical signs of lethargy, piloerection, excessive grooming and vocalization, and there was a single death (1/5 males, 0/5 females). In rats, a single dose of 2 mg/kg was considered by the sponsor to be the maximum tolerated dose based on mortality and clinical signs. Clinical signs included lethargy, pale ears, dyspnea, hyperapnea, ataxia and hind-leg paralysis. However, once again, there was a single death (1/6 males, 0/6 females).

Repeat Dose Toxicity

Terlipressin diacetate pentahydrate was administered intravenously to rats and dogs for up to 28 days followed by a 2 week post dosing period to assess the reversibility of any effects observed.

Rats

Acute mortality was seen for terlipressin-dosed rats. Most deaths occurred within the first hour of the first day of dosing and were dose-dependent. In a 7 day dose range-finding study, 4/9 males and 2/9 females receiving 2 mg/kg died within an hour of dosing on day 1. In the 28 day study, the high dose (1.5 mg/kg) was split into two daily doses and administered 1 to 2 hr apart. Most deaths (22 of 26) in this study occurred on the first day of dosing. The remaining deaths occurred on the 2nd (3 animals) and 3rd day of dosing. The mortality was dose-dependent (1/49, 6/54 and 29/59 (including replacement animals) at 0.15, 0.5 and 1.5 mg/kg/day, respectively) with a much higher incidence in males (23) than females (3). The cause of death, according to the sponsor, was most likely pulmonary edema and/or hemorrhage due to reduced perfusion as a result of the vasoconstrictive action of terlipressin. However, no necropsy was done. After each dose, animals exhibited clinical signs such as lethargy, dyspnea, hyperapnea, ataxia and hind-leg paralysis that lasted for an hour. None of these signs were observed during the 2 week recovery period. A statistically significant but nondose-dependent reduction in body weight gain relative to control was observed for males at doses as low as 0.15 mg/kg/day from study day 7 onwards. A statistically significant decrease in erythroid parameters was noted in males and females receiving 1.5 mg/kg/day. Significant ($p < 0.05$) and nondose-dependent decreases in mean kidney and testes weights (both absolute and relative to final body weight) relative to control were noted for males at 0.15 or more mg/kg/day in the 7 day and 28 day studies. In females, thymus weights (both absolute and relative to body weight) were reduced ($p < 0.05$) relative to control at all doses. Noteworthy histopathologic findings were observed in the kidneys, testes and thymus as early as 7 days. A dose-dependent nephritis, probably ischemic in origin, was noted in both sexes at doses as low as 0.15 mg/kg/day (absent in control group). These lesions consisted of multifocal tubular dilation in the cortex with some non-suppurative interstitial inflammation and fibrosis. Evidence of trace nephritis was noted at the end of the 2 week recovery period in the lone surviving male receiving 1.5 mg/kg/day. A dose-dependent (mild to moderate to severe) seminiferous tubular degeneration of the testes was noted at doses of 0.5 or more mg/kg/day. In the recovery group animals, severe and moderate seminiferous tubular degeneration was still noted in 1/4 mid and 1/1 high dose males, respectively. A nondose-dependent (trace to mild) cortical lymphoid depletion of the thymus was observed at doses as low as 0.15 mg/kg/day in both males (not observed in 7 day study) and females (in both 7 day and 28 day studies). These findings were absent in control animals in the 7 day study but were present at a lower than treatment group incidence in control animals in the 28 day study. At the injection site, perivascular inflammation was noted sporadically in treated but not control animals. The thymus was normal and the injection site was free of inflammation in all recovery group animals.

Dogs

No mortality was seen for terlipressin-dosed dogs. Based on the severe clinical signs noted in a 7 day dose range-finding study, all doses (0.0625 or more mg/kg/day) for the 28 day study were divided and administered 6 hr apart. Clinical signs included pale gums, lethargy, emesis and defecation; the incidence and severity were dose-related. The signs abated within 30 to 60 min

post dose, were less severe following the second dose on the first day and were largely absent following subsequent doses. A dose-dependent decrease in body weight gain (7 to 19% relative to control) was noted for males at doses of 0.0625 or more mg/kg/day. A dose-dependent decrease in mean absolute but not relative kidney weight was noted for males at doses as low as 0.0625 mg/kg/day. Histopathological lesions in the kidney (minimal to mild multifocal chronic cortical nephritis, interstitial lymphocytic infiltration, and/or tubular dilation) were seen in a dose-related manner in both males and females. Trace nephritis was also noted in a male dog after a 2 week recovery period. These findings were absent in control animals. Perivascular inflammation, hemorrhage and edema at the injection sites were noted in both treated and control groups. However, these were absent after the recovery period. A nondose-dependent mild pulmonary inflammation was found in 14/18 terlipressin-dosed animals and one of six control dogs.

Genotoxicity

Terlipressin was not mutagenic in the Ames reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay and *in vivo* mouse micronucleus test.

Toxicokinetics

Terlipressin is a pro-drug and is rapidly converted to lysine vasopressin. Both terlipressin and lysine vasopressin are rapidly eliminated with half lives in rats of 0.2 and 1.9 hr, respectively (not calculable in dogs). There was no evidence of accumulation of either of these compounds after repeat doses, which is consistent with their rapid elimination. According to the sponsor, terlipressin Cmax at the lowest dose studied in the 28 day rat study (LOAEL dose) was about 3- to 6-fold higher than that seen in HRS patients treated with 1 to 2 mg terlipressin. Terlipressin Cmax at the lowest dose studied in the 28 day dog study (LOAEL dose) was similar to that seen in HRS patients (Table 4.1). However, this reviewer finds exposure data (both animal and human) insufficient for estimating safety margins and recommends that animal and human doses be compared on a body surface area basis. On that basis, the lowest dose of terlipressin studied in rats was about 1- to 2-fold higher than that observed in HRS patients (dosed at 1 to 2 mg). The lowest dose studied in dogs was 0.7- to 1.5-fold that observed in HRS patients. It should be noted that a NOAEL was not demonstrated in either the rat or dog.

TABLE 4.1
COMPARISON OF ANIMAL AND HUMAN EXPOSURE TO TERLIPRESSIN AND LYSINE VASOPRESSIN FOLLOWING INTRAVENOUS ADMINISTRATION OF TERLIPRESSIN

Species (study)	Terlipressin dose administered (mg/kg)	Total daily dose (mg/kg)	Duration of dosing	n	Terlipressin exposure			Lysine-vasopressin exposure		
					T_{max}[a] (min)	C_{max}[b] (ng/mL)	Approx fold-difference vs human (1-2 mg)	T_{max} (min)	C_{max}[b] (ng/mL)	Approx fold-difference vs human (1-2 mg)
Preclinical Toxicokinetic Studies										
Rat (CB05-5121-R-TX)	2 QD	2	7 days	3	15	149	NA[c]	15	425	30-60
Rat (CB06-5013-R-TX)	0.75 BID	1.5	28 days	2	5	5385	40-90	5-10	75	50-100
	0.5 QD	0.5		2	5	1078	10-20	5-10	21.5	15-30
	0.15 QD[d]	**0.15**		**2**	**5**	**352**	**3-6**	**5-10**	**9.25**	**7-12**
Dog (CB06-5030-D-TX)	0.15 BID	0.3	7 days	4	5	293	2-5	15	10.6	8-14
Dog (CB06-5089-D-TX)	0.125 BID	0.25	28 days	4M	5	392	3-12	30	8.99	7-17
				4F	5	761		30	12.89	
	0.0625 BID[d]	**0.125**		**3M**	**5**	**429**	**1-7**	**30**	**1.76**	**1-3**
				3F	**5**	**198**		**30**	**1.89**	
	0.031 BID	0.0625		3M	5	72	0.5-2	15	1.04	1-4
				3F	5	132		15	2.80	
Clinical Pharmacology Study (Population PK)										
Human (OT-0401 Population PK)	1 mg QID (0.01 mg/kg)[e]	0.04	Up to 14 days	29	5	62[f]	-	7	0.75[g]	-
	2 mg QID (0.02 mg/kg)[e]	0.08		10	5	138[f]	-	30	1.38[g]	-

QD=once per day; BID=twice per day; QID=4 times per day
a: Earliest timepoint measured
b: Mean values
c: NA – not applicable because terlipressin was measured at 15 min in this study compared to 5min (T_{max}) in humans.
d: NOAEL dose
e: Dose in mg/kg terlipressin base. In study OT-0401, the 1 and 2 mg doses represent 1 mg terlipressin acetate (equivalent to 0.85 mg terlipressin peptide) and the median body weight was 85.9 kg. The doses in the animal studies represent mg/kg terlipressin base.
f: Terlipressin C_{max} calculated from population PK model.
g: Lysine-vasopressin C_{max} is averaged non-modeled values.

Evaluation

The hemodynamic effects of terlipressin reported in numerous animal models are consistent with the effects reported in clinical studies. The proposed mechanism of action of terlipressin in HRS patients is to produce vasoconstriction of the dilated splanchnic arterial blood to cause increased arterial blood volume and blood pressure, which results in an increase in renal perfusion and improved renal function. The toxicological study findings in rodents and dogs are consistent with the known pharmacologic effects of terlipressin and its active metabolite lysine-vasopressin, effects which are mediated through V_1 receptor activity (severe vasoconstriction resulting in reduced perfusion) at the high doses studied. A large number of deaths and severe adverse effects occurred in rats within the first 3 days of dosing. The effects were dose-dependent and reduced by splitting the daily dose into two. A NOAEL could not be determined in the repeat dose studies. Males appeared to be more sensitive to terlipressin toxicity than females, though there was no difference in systemic exposure between the sexes.

The major organ affected by terlipressin in rats and dogs was the kidney. Abnormalities found in the kidneys (multifocal chronic cortical nephritis, interstitial lymphocytic infiltration and/or tubular dilatation) were dose-related and reversible. Other toxicological findings noted in rats were pulmonary congestion and inflammation of the lungs (in early deaths), decrease in testes

weight with seminiferous tubular degeneration, and mild cortical lymphoid depletion of the thymus. The latter effect is considered to be an indication of stress.

Terlipressin has no mutagenic or clastogenic activity. Adverse effects of AVP and terlipressin in animal and human pregnancies have been well described in the literature and include increased uterine contractility and reduced blood flow to the uterus and placenta, resulting in fetal death and/or abortion. No new reproduction/developmental toxicity studies have been done by the sponsor. Thus, in accordance with 21CFR201.57, the sponsor proposes that terlipressin be labeled as (b) (4) (b) (4)

The duration of action of terlipressin is longer than that of AVP due to the gradual conversion to lysine vasopressin. The initial plasma concentration of terlipressin following IV administration is about 100-fold higher than the peak concentration of lysine vasopressin. But terlipressin has only about 1% of the V_1 activity of lysine vasopressin. Hemodynamic effects in humans were seen at doses of about 7.5 to 30 µg/kg compared to doses of 2 to 90 µg/kg in rats and 20 to 100 µg/kg in dogs. The pharmacological activity of terlipressin is similar in humans and the species used in the safety evaluation studies and, according to the sponsor, the animals and humans respond to similar concentrations of terlipressin. Systemic exposure data from the toxicity studies in animals and systemic exposure data for humans are, however, inadequate for establishing safety margins for the adverse effects observed in animals. When comparisons are based on body surface area adjusted dose levels, the lowest terlipressin dose level studied in rats (LOAEL dose) was about 1-2 times higher than that studied in HRS patients (1-2 mg). In dogs, the lowest dose studied (LOAEL dose) was 0.7 to 1.5 times that studied in HRS patients. Though there is little if any safety margin for the adverse findings observed in dogs and rats, the short half-life (approximately 1 hr) and duration of therapy (14 days), and the extensive, published clinical experience with this drug suggest that terlipressin can be used safely for the treatment of HRS type1 at the proposed therapeutic dose in accordance with the proposed product labeling.

Recommendations on Labeling: See page 5.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22231	ORIG 1		LUCASSIN (TERLIPRESSIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GOWRA G JAGADEESH
08/06/2009

Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-4079

Memorandum

DATE: June 30, 2009

FROM: Nancy Xu and John Lawrence
TO: NDA 22-231, S-014
SUBJECT: Terlipressin

This is a review of submission 014, dated April 30, 2009, which was the sponsor's response to the clinical and statistics Disciplinary Review Letter from the Agency. The Disciplinary Review Letter related to the sponsor that the clinical and statistical reviewers found the results not compelling, specifically the single pivotal trial failed on the pre-specified primary and secondary endpoints. Please also see the clinical and statistical cross-disciplinary review for details.

In the sponsor's response, the sponsor argues that their exploratory endpoint, a transient reduction in serum creatinine, in the presence of increased ischemic events, and without any demonstrable survival benefit constitutes a favorable benefit to risk profile. The sponsor submitted the following arguments. The reviewers' response, in italic, is listed below each of the sponsor's argument.

1) The sponsor asserts that the two submitted randomized, controlled studies (OT-0401 and TAHRS) support a "favorable clinical benefit" of terlipressin in the treatment of "HRS type I".

To support the claim, the sponsor submitted two studies, a double-blind, placebo-controlled pivotal study (OT-0401), and an open-label safety study (TAHRS). TAHRS was a small open-label, cross-over study in HRS I (n=17) and II (n=6) patients. Please see p39 of the clinical and statistical cross-disciplinary review regarding "limitations of TAHRS for Support Approval of Terlipressin for HRS type I".

2) In the pivotal trial, HRS reversal, a one time reduction in serum creatinine at or below 1.5 mg/dL, was defined before database closure and unblinding on June 12, 2006. To support their assertion, the sponsor provided internal e-mail communications between the statistician and the sponsor dated May 17, 2006, discussing ways to perform the statistical plan for "an additional SCr table", an exploratory analysis with at least one SCr $\leq$1.5.

The provided internal email does not provide reasonable reassurance that the sponsor did not explore different versions the exploratory analysis and ultimately chose the one with the lowest p value. Furthermore, the sponsor has not provided any proof that the database closure and

unblinding was indeed on June 12, 2006. In the pivotal trial, the last patient was enrolled on March 10, 2006, and therefore, the 14-Day study treatment data collection for the primary endpoint was completed by March 24, 2006. In the sponsor's official statistical plan dated June 9th, 2006, the sponsor still defined "HRS reversal" as serum creatinine values "at or below 1.5 mg/dL, with at least two measurements 48+/-8 hours apart". The date of the submitted HRS reversal statistical algorithm requiring only one such measurement was on August 31, 2006. Lastly, unlike the sponsor's other endpoints, Treatment Success, Treatment Failure, or Partial Response, the sponsor's HRS reversal statistical algorithm (August 31, 2006) excludes SCr values on the same day of transplant even when the SCr values reflect study treatment effect and were measured prior to liver transplantation. By applying this exclusion criterion, a placebo patient (120-01) with a SCr value of 1.5 mg/dL obtained while on study treatment and prior to liver transplantation was excluded for receiving a liver transplant subsequently on that date of SCr measurement. If counting 120-01 as HRS reversal, the p value changes from 0.008 to 0.027. This is serves as an example of variations in the definition of the endpoint that can affect the p value.

3) The primary endpoint for regulatory evaluation was changed post-trial completion in agreement with FDA.

In contrast to the sponsor's assertion, FDA did not agree that the primary endpoint could be changed post-trial completion after knowing the results of the pivotal trial OT-0401. During the pre-NDA meeting (November 22, 2006), the sponsor reviewed the study results of OT-0401 with the FDA. FDA found the results not compelling. Dr. Temple related that FDA does not accept a one-time improvement in SCr that then goes away. FDA advised that the sponsor should plan on demonstrating effectiveness on a primary endpoint (sustained improvement in SCr) in two studies at $p<0.05$. Furthermore, in the context of discussing an additional trial, Dr. Temple recommended a double-blinded study. In short, HRS reversal defined as one or more SCr at or below 1.5 mg/dL while on treatment includes a one-time improvement in SCr and fails to follow the FDA guidance.

4) The sponsor considers the magnitude of transient effect on SCr to be clinical significant for the following reason.
a) The reversal of HRS type I represent a major clinical response to treatment: for the endpoint to be achieved the rapid progression of renal failure is stopped and the patient's renal function is normalized.

A one time reduction in SCr that subsequently goes away, particularly without any compelling evidence of benefit to the patient, does not constitute a clinically meaningful endpoint.

Furthermore, a decrease in SCr does not necessarily represent a reversal of HRS type I in your study population where the diagnosis of HRS type I could not be independently verified to rule out inclusion of subjects with spontaneously reversible or more reversible causes of renal insufficiency (see p8 the medical statistical review). This point is important because while HRS type I is associated with irreversible renal impairment and high mortality, other causes of renal impairment in cirrhosis are NOT.

b) Although not all patients achieve the key endpoint of HRS reversal, in Study OT-0401 a significantly higher number of terlipressin patients achieved this endpoint as compared to control (Table 1). A similar significant effect was observed in the TAHRS Study.

Sponsor's Table 1. Improvement of Renal Function by Terlipressin - OT-0401 and TAHRS (ITT)

Endpoint	OT-0401			TAHRS		
	Terlipressin (N=56)	Placebo (N=56)	P-value	Terlipressin + Albumin (N=23)	Albumin (N=23)	P-value
HRS reversal, n (%)	19 (33.9)	7 (12.5)	0.008 [a]	9 (39.1)	2 (8.7)	0.018 [a]
Change in SCr, (mg/dL)						
Days 1-14: Overall	-0.7 (0.19)	0.0 (0.19)	0.009 [b]	——	——	——
Day 1 - End of Treatmt: Overall	-0.7 (0.18)	0.0 (0.19)	0.003 [b]	-0.28 (0.23)	+0.41 (0.23)	0.031 [b]
Change in SCr from baseline through Day 14 (OT-0401) or end of treatment (OT-0401, TAHRS) shown as least squares (LS) mean with standard error (SE). a: From a stratified CMH test. b: From Repeated Measures ANOVA as implemented in Proc Mixed with factors Treatment, Day, Strata and Treatment by Day.						

All of the above endpoints presented for the pivotal OT-0401 were not prespecified. When the primary endpoint fails to show a significant difference, any post hoc analyses or secondary endpoints can only be interpreted as exploratory or hypothesis generating.

The change in SCr from Day 1 through Day 14 is not a pre-specified secondary endpoint. The pre-specified secondary endpoint evaluates the change from baseline (pre-study drug) to Day 14 (i.e. a single time point). The change in SCr from Day 1 to end of treatment is an exploratory endpoint. The prespecified analysis of the change in SCr from baseline to Day 14 yielded a statistically non-significant p value. Please see our review of the OT-0401 (p21-27) on all the primary and secondary endpoints evaluated in the trial.

c) In Study OT-0401, transplant-free survival was significantly longer in terlipressin-treated patients with HRS reversal vs. nonresponders. These data illustrate an improved clinical outcome associated with reversal of the acute renal failure (see Supportive Data document, Figures 1 and 2). A similar effect was observed in the TAHRS Study.

This analysis demonstrates that a reduction in SCr in response to either placebo or terlipressin is associated with improved clinical outcome. It is conceivable that SCr reduction is a marker of improving underlying condition (e.g. occult infection that is treated). However, this analysis does not prove that terlipressin is more effective than placebo in improving clinical outcome.

d) The overall average change in SCr from baseline through Day 14 and/or end of treatment was evaluated as a secondary endpoint. The terlipressin group in both studies experienced a

significant reduction in SCr from baseline relative to placebo/control. The magnitude of this change in SCr (~0.7 mg/dL in both studies) exceeds that considered to be clinically relevant (change of 0.3 mg/dL) by the medical community (Mehta 2007, Coca 2007).

Coca 2007 is a systemic review and meta-analysis of 7 published studies: 4 retrospective, 2 prospective, and 1 retrospective subgroup analysis of two randomized control trials. None of these studies were in HRS. Lassnigg 2004 and Levy 2005, the studies in the meta-analysis that provided time frame of the changes in SCr, showed that abrupt increases in SCr within 48 hours was associated with increased mortality. However, unexpectedly, decreases in SCr greater than 0.3 mg/dL within 48-hours after cardiac and thoracic aortic surgery was also found to be associated with higher 30-day mortality (Lassnigg 2004). In fact, a U-shaped relationship between changes in SCr (x-axis) and 30-day mortality (y-axis) exists.

The Acute Kidney Injury Network (AKIN) (Mehta 2006) proposes a consensus definition of acute kidney injury (AKI). In this publication, an absolute increase in SCr ≥ 0.3 mg/dL within 48 hours, under optimal state of hydration, is among the several definitions of AKI. However, it is not clear whether the AKI definition applies to hepatorenal syndrome. Furthermore, this article also acknowledges that "current clinical practice does not focus much attention on small increments (e.g. 0.3 mg/dL) in SCr" which can be attributed to lab variations and the small absolute cut-off may "increase false-positives." Therefore, taken together, there is insufficient evidence from the literature to judge whether a 0.7 mg/dL SCr reduction over a longer time period, 14-days, is associated with a clinical benefit, particularly in HRS.

e) The 17 published trials of terlipressin in the treatment of HRS also demonstrated similar clinically significant reductions in SCr (see Supportive Data document, Appendix 1). The seventeen published studies in approximately 300 HRS (that is HRS type I and II) patients that showed terlipressin use is associated with/lead to a transient reduction in serum creatinine.

Of the 17 submitted studies, 9 are uncontrolled, open-label studies (Angeli 2006, Mulkay 2001, Sanner 2004, Uriz 2000, Colle 2002, Danaliglu 2003, Duhamel 2000, Moreau 2002A, Niemczyk, 2006), 7 are retrospective (Restuccia 2004, Colle 2002, Danaliglu 2003, Duhamel 2000, Halimi 2002, Moreau 2002A, Niemczyk, 2006). Of the 4 randomized, controlled trials (Hadengue, 1998, Solanki, 2003, Neri 2007, Yang 2001), 3 used albumin as concomitant medication, though dosages were different in the studies. One used furosemide in the control arm. Only two studies were focused on HRS type I.

Seventeen studies with terlipressin were only able to demonstrate a transient reduction in serum creatinine compared with either baseline SCr or controls. None of the studies reported a sustained improvement in SCr, or any morbidity or mortality benefit.

5) The clinically and statistically significant effect of HRS reversal to have been sustained in the majority of patients for the following reasons:
a) Based on the natural history of HRS type 1, there is no spontaneous reversal without treatment. Since the goal of terlipressin treatment is to reverse HRS type 1, the sponsor considers the lack of HRS type 1 recurrence to be the most clinically relevant measure of long term success. If the effect of terlipressin was transient, there would be a high rate of early recurrence

of HRS type 1 within 30-60 days following the cessation of terlipressin therapy. The observed low rate of recurrence demonstrates that the effect of terlipressin is sustained in the majority of patients.

Please see earlier response that we can not independently verify your diagnosis of HRS type I. Also, recurrence rate was also low in your placebo arm. Only one of the 8 responders in placebo group had recurrence.

b) The overall sustained effect of terlipressin on SCr as compared with placebo is depicted in Figure 2 below. As per the Study OT-0401 protocol, SCr values were only collected from patients while they were on study treatment and on Day 14. If a patient terminated treatment due to treatment response, treatment failure (SCr at or above baseline by Day 7 or need for dialysis), transplant, AE or death, then SCr values were no longer collected. Figure 2 uses the last observation carried forward (LOCF) method to incorporate the full population of treated patients.

Figure 1: Mean Change from Baseline in SCr (mg/dL) by Study Day Through the End of Treatment (Last Observation Carried Forward, ITT)

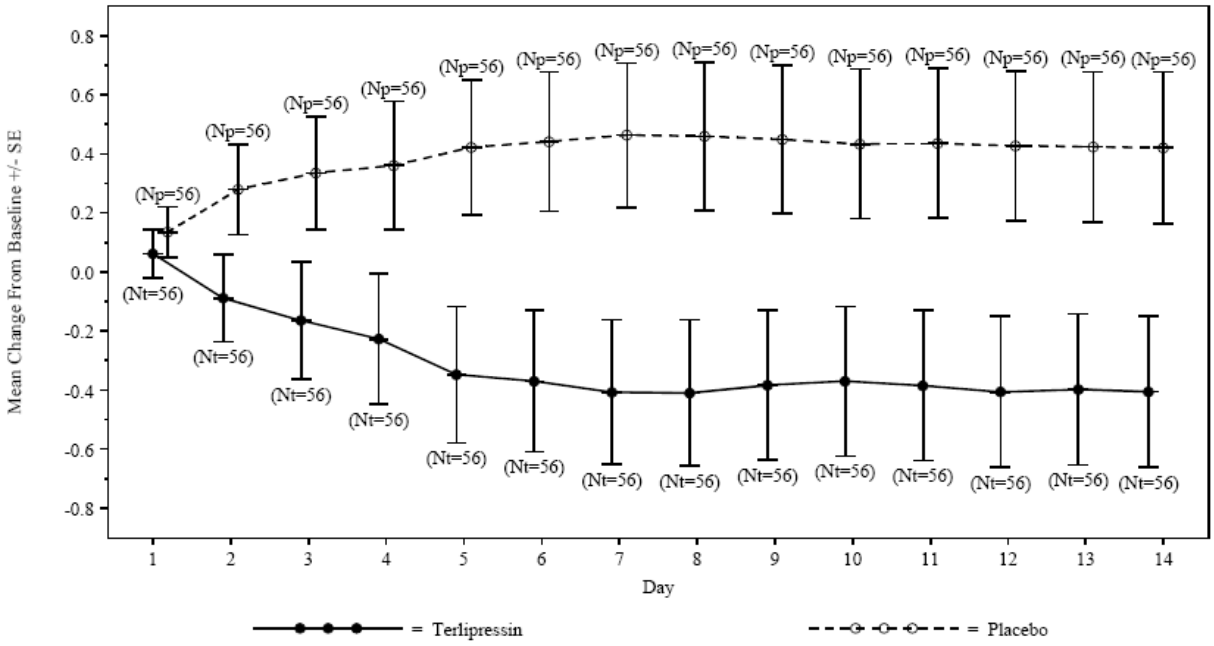

Figure 2, which uses the LOCF method, accounts for the SCr levels of the discontinued patients, and is therefore considered to be an appropriate means to summarize the overall effect of terlipressin vs. placebo during the study treatment period.

The reviewers do not concur with this use of the LOCF analysis. In the case of missing data, this analysis assigns SCr to be the same as the values at the last observation for subsequent days by assuming that the SCr stays constant. In reality SCr is unlikely to remain the same in this critically ill population, particularly those who drop out for Treatment failure or AE. In addition, there are issues regarding your of baseline measurement values delineated in our review on page 9, "non-uniform determination of baseline SCr value".

6) Serum creatinine (SCr) is an "objective and direct measurement of renal function."

SCr concentration is a function of creatinine generation and elimination. In liver disease, malnutrition, and possibly impaired synthesis of creatine (Silva 2008), lead to lower muscle mass, and lower than expected serum creatinine in the setting of renal disease. SCr concentration is currently used to estimate GFR in cirrhosis because more accurate measures of GFR are more expensive and might not be universally available, Nonetheless, it is well recognized that SCr is a suboptimal measure of GFR in cirrhosis (Gines 2003). Therefore, the position that SCr is an objective measurement of renal function is arguable in cirrhosis.

7) Higher SCr for a longer period of time predicts worse outcome in liver disease, specifically in HRS, and worse outcome post-transplantation (Cabezuelo 2006, Campbell 2005, Contreras 2002, DuCheyron 2005, Lafayette 1997, Moreno 2003).

The cited retrospective studies suggest that a higher SCr, or the duration of a higher SCr but not a level of SCr per se, regardless of cause, are either associated with or predictive of worse outcome post-transplantation. However, the cited studies do not show that therapies that lower SCr are associated with improved morbidity or mortality.

8) HRS prior to transplantation represents a risk factor for higher morbidity and mortality after transplant; reversing renal dysfunction prior to transplant may improve the patient's overall clinical outcome (Gonwa 1995, Restuccia 2004).

The two cited references help generate the hypothesis that reversing renal dysfunction prior to transplant may improve the patient's overall clinical outcome after transplantation. However, neither of the submitted treatment trials, OT-0401 or TAHRS, provided any compelling evidence for "reversing renal dysfunction" or any clinically meaningful post-transplant outcome benefit with terlipressin as compared to placebo.

9) Published literature supports that rapid reduction of SCr in acute renal failure of HRS type 1 is associated with an overall improved patient clinical outcome. The goal of terlipressin treatment is to both reduce the amount of time a patient has a severely elevated SCr and the magnitude of that elevation, essentially the "area under the curve" of renal dysfunction for that patient.

The submitted literature generates a hypothesis that treatment of HRS type I with terlipressin can lead to better patient outcome through decreasing the "area under the curve" of renal dysfunction. Neither the literature, nor the submitted trials, has provided any direct proof of this hypothesis.

10) HRS type I is a rare, life-threatening condition with high mortality rate (>80% over 3 months) and no available pharmacological therapy approved in the US. Although terlipressin improves renal function, it does not affect the underlying severe liver disease, and thus can only be expected to have a modest effect on overall survival. Given the observed overall relative survival difference of 14% at the 180 Day follow-up (42.9% for terlipressin patients vs. 37.5% for placebo patients, *p*=NS), a much larger sample size (~2000 patients) would be required to

adequately power a study to demonstrate a survival difference. However, a placebo-controlled study of this size is not feasible considering the rarity of HRS type 1.

The 17 referenced literature (see comment in section 3e) and the two submitted clinical trials, OT-0401 and TAHRS, did not demonstrate any improvement in morbidity or mortality of terlipressin over placebo. In fact, the studies showed a higher incidence of ischemic complications in terlipressin group as compared to placebo. Furthermore, the direction of the change in mortality comparing terlipressin vs. placebo can not be predicted based on the data given. TAHRS was terminated after an interim analysis found higher 3-month mortality on terlipressin as compared to placebo (27% vs. 19%). Arguably, with a larger sample size, there is also a potential of demonstrating a higher mortality in terlipressin as compared to the placebo.

Lastly, two retrospective studies by Esrailian 2007 (n=60, HRS type I) and Skagen 2009 (n=162, HRS) suggest that other vasoconstrictors combinations, octreotide and midodrine, when used with albumin improve survival and reduce SCr compared to control, at significantly lower sample size than suggested by the sponsor. Therefore, it might be possible to show a difference in survival with a reasonable sample size if a drug is truly effective in improving survival.

11a) In the double-blind, placebo-controlled study, OT-0401, there was a small incremental increase in AEs with terlipressin relative to placebo (93% vs. 89%) and the incidence of SAEs in both groups was identical (66%).

While the number of adverse event experience per person is similar, more treatment emergent adverse events were experienced in the terlipressin group. Please see the medical and statistical review page 33 to 34.

11b) The AEs, including, myocardial infarcts and intestinal ischemia, experienced by terlipressin patients were predictable, manageable and reversible.
Myocardial infarct is not reversible. This is troubling in a study group which excluded subjects with significant cardiac history. Intestinal ischemia and the resultant necrosis can be life-threatening. These ischemic complications are not trivial, particularly in the critically ill patients with HRS type I. Please also refer to the following sections in the combined medical and statistical review: p9 "inconsistent and incomplete OT-0401 survival information", p10 "improper attribution of adverse events to placebo in subjects who later crossed-over to terlipressin treatment", p27-36 "OT-0401 safety outcomes", p44-46 "TAHRS survival outcomes", and p47 "the incidence of serious treatment emergent AE". In the medical reviewer's opinion, the two submitted studies have not demonstrated a favorable benefit to risk ratio.

12) Based on the totality of the NDA study data, the sponsor conclude that the dosing regimen used in Study OT-0401 is safe and efficacious for the treatment of HRS type 1 (1 mg every 6 hours increased to 2 mg every 6 hours if SCr decreased <30% after 3 days):

- Although no formal dose-finding studies were conducted due to the rarity of the patient population, the dosing regimen studied in OT-0401 was based on a substantial body of evidence from 11 literature studies where effective doses of terlipressin in HRS type 1

ranged from 2 to 12 mg/day. (b) (4)

(b) (4)

- Two dose intensities were studied in the phase 3 program: 1-2 mg every 6 hours (Study OT-0401) and 0.5-2.0 mg every 4 hours (TAHRS Study).
- The OT-0401 dosing regimen had a less frequent dosing interval and lower daily dose intensity than the TAHRS Study regimen, but resulted in similar efficacy and a lower rate of SAEs and withdrawals due to AEs (Table 4).

Based on the totality of evidence, the medical and statistical reviewers conclude that the appropriate dose, duration of terlipressin and concomitant albumin to achieve a clinically meaningful endpoint have not been established. Neither trials, OT-0401 or TAHRS, achieved a clinically meaningful endpoint. Furthermore, in the OT-0401 trial, whether to administer and the amount and duration of albumin administered are at the discretion of the investigator. As a result, only 23 subjects in either the terlipressin and placebo group started albumin the same date as the study medication, and only 2 subjects in placebo and 4 subjects in terlipressin group received albumin on the same dates and duration of the blinded study medications.

Furthermore, it is not always clear whether the albumin was administered temporally within the 14 days period of study medication were intended for the treatment of hepatorenal syndrome. For less than half of the subjects, the recorded indications for albumin administration were "hepatorenal syndrome, liver disease, liver cirrhosis, renal failure, as study medication, concomitant with study drug, or per protocol". The rest of the subjects received the albumin for purposes that appear unrelated to the treatment of hepatorenal syndrome. Those indications included "therapeutic or large volume paracentesis, intra-operative fluid volume control, blood loss, hypovolemia, volume replacement, intravascular volume maintenance, hypotension, volume expander, hypoalbuminemia, and protein replacement". The prescribed total daily dose and the administration regimens are widely different. The prescribed regimen ran the gamut of dosages: as needed, as a single dose, for a few doses, daily dose preceded or not preceded by bolus, twice, three times or four times daily, and a number range from 4 to 10 packs per day. Lastly, the actual administered daily dose or the total dose over the treatment period can not be determined because the actual dose time and number of times the dose were actually administered were not provided in a database.

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/s/

Nancy N Xu
6/30/2009 10:58:26 AM
MEDICAL OFFICER

John Lawrence
6/30/2009 11:10:26 AM
BIOMETRICS

James Hung
6/30/2009 10:28:40 PM
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