CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

TERLIPRESSIN BRIEFING DOCUMENT

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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ABC	ATP-binding cassette
ACLF	acute-on-chronic liver failure
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
BID	twice daily
BL	baseline
CAD	coronary artery disease
CLIF-SOFA	Chronic Liver Failure-Sequential Organ Failure Assessment (score)
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRL	complete response letter
CSR	clinical study report
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EVH	esophageal variceal hemorrhage
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good laboratory practice
HPVG	hepatic venous pressure gradient
HRS-1	hepatorenal syndrome type 1
ICA	International Club of Ascites
ICA-AKI	International Club of Ascites-acute kidney injury
IND	Investigational New Drug
ICU	Intensive care unit
INR	international normalized ratio
ITT	intent-to-treat
IV	intravenous
LS	least squares
LVP	large volume paracentesis

MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
ML	maximum likelihood
MODS	multiple organ dysfunction syndrome
MOF	multi-organ failure
MTD	maximum tolerated dose
NDA	New Drug Application
NNH	number needed to harm
NNT	number needed to treat
OR	odds ratio
PD	pharmacodynamics
PI	package insert
PK	pharmacokinetics
q4h	every 4 hours
q6h	every 6 hours
QTc	corrected QT interval
QTcF	QTc using Fridericia's formula
RRT	renal replacement therapy
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SE	standard error
SIRS	systemic inflammatory response syndrome
SLC	solute carrier
SMQ	Standardised MedDRA Query
SPA	Special Protocol Assessment
SOC	System Organ Class
TIPS	transjugular intrahepatic portosystemic shunt
UNOS	United Network for Organ Sharing
US	United States
WBC	white blood cell
WHO	World Health Organization

1 EXECUTIVE OVERVIEW

- Hepatorenal syndrome type 1 (HRS-1) is an acute functional renal failure in the setting of decompensated cirrhosis.
- HRS-1 is a life-threatening complication requiring immediate intervention.
- The immediate goals of treatment for patients with HRS-1 are acute improvement in renal function and reversal of the functional renal failure.
- Currently, there is no approved treatment for HRS-1 in the United States (US) to improve the care of these critically ill patients.
- Outside of the US, terlipressin is approved in 24 countries for over 10 years for the treatment of HRS-1 and is recommended as first-line treatment in international treatment guidelines (eg, International Club of Ascites, 2015 and European Association for the Study of the Liver, 2018) for the treatment of HRS-1.
- Terlipressin is an acute, short-term therapy that effectively improves renal function, reverses the pathophysiology of HRS-1, and improves clinically meaningful outcomes, such as reduced need for renal replacement therapy (RRT) and reduced intensive care unit (ICU) stay, in patients with HRS-1.
- The efficacy and safety of terlipressin are demonstrated in 2 randomized, placebo-controlled studies: the pivotal CONFIRM study and the supportive phase 3 OT-0401 study, with additional data provided by a third phase 3 study, REVERSE.
- Together, these 3 studies provide the largest prospective database for any intervention for the rare condition of HRS-1.
- The safety profile of terlipressin is well characterized, with the majority of adverse events (AEs) being predictable, recognizable, and manageable in the hospital setting where terlipressin is used.
    - Patients with the most advanced renal dysfunction (ie, baseline serum creatinine [SCr] ≥ 5 mg/dL) have a lower likelihood of achieving HRS-1 reversal, experience a higher incidence of severe, serious, and/or fatal AEs, and have a higher 90-day mortality. Thus, in order to optimize the benefit-risk of terlipressin, terlipressin use is not recommended in these highly compromised patients.
    - Respiratory failure, which may become complicated by events of sepsis and can lead to death, is a known risk with terlipressin use. The Sponsor has developed a risk mitigation plan that, when implemented, is expected to help identify those patients who may be at greater risk and to reduce the likelihood of progression to severe respiratory events.

- The proposed mitigation strategy, by facilitating identification and proper management of high risk patients, as well as limiting the use of terlipressin in patients with the most advanced renal failure (ie, baseline SCr ≥ 5 mg/dL) further improves the benefit-risk profile of terlipressin in patients with HRS-1.

1.1 Introduction

Hepatorenal syndrome type 1 (HRS-1) is a rare, acute complication of decompensated cirrhosis that results from hemodynamic changes causing vasodilation in the splanchnic bed. The vasodilation culminates in a reactive vasoconstriction of the renal artery. This life-threatening condition requires rapid intervention; however, there is no proven or approved pharmacological therapy available to patients with HRS-1 in the US. Terlipressin has been available to patients in >40 countries for >30 years for the treatment of esophageal variceal hemorrhage (EVH), and, with the concomitant administration of albumin, is the standard-of-care for HRS-1 where approved (24 countries for >10 years). In addition, terlipressin is the recommended treatment for HRS-1 in internationally recognized treatment guidelines, such as those published by the European Association for the Study of the Liver (EASL 2018) and International Club of Ascites (ICA, Angeli 2015a).

To address this unmet medical need in the US, Mallinckrodt Pharmaceuticals has developed terlipressin for injection as an acute therapy for the indication of "the treatment of adults with hepatorenal syndrome type 1."

The terlipressin clinical program comprised 3 randomized, placebo-controlled studies comparing terlipressin to placebo. The regulatory basis for approval is based on the recently completed pivotal CONFIRM study, which achieved its primary endpoint, along with the original OT-0401 supportive study, which provides confirmatory evidence of efficacy. Additional efficacy and safety data are provided by the REVERSE study. Although REVERSE did not achieve statistical significance for the primary endpoint, it showed improvement in renal function in terlipressin-treated subjects.

The primary efficacy endpoint of CONFIRM, Verified HRS Reversal, was developed in consultation with and agreed to by the US Food and Drug Administration (FDA) through a Special Protocol Assessment (SPA) procedure. The study achieved the primary efficacy endpoint and demonstrated a significantly higher rate of Verified HRS Reversal with terlipressin than with placebo (p=0.012). The study showed additional clinically meaningful benefits of improvement in renal function (more than twice as many patients receiving terlipressin achieved a ≥30% improvement), reduction in the requirement for RRT (15 percentage points lower at each time point of assessment), and a shorter length of ICU stay (reduction by half of the length of stay compared with placebo).

The safety profile of terlipressin is well characterized in the clinical program, with the majority of AEs being predictable, recognizable, and manageable in the hospital setting in which HRS-1

patients are treated. As expected for these critically ill patients, the incidence of AEs, serious AEs (SAEs), and mortality was high with both terlipressin and placebo in the integrated safety population of the 3 placebo-controlled studies. There was an increased risk of respiratory events with terlipressin treatment, and terlipressin should be used with caution in patients with dyspnea, tachypnea, or respiratory distress; patients should be closely monitored for pulmonary edema.

Respiratory failure, which may be complicated by associated events of sepsis and can lead to death, is a known risk with terlipressin use. The Sponsor has developed a risk mitigation plan that, when implemented, is expected to help identify those patients who may be at greater risk and to reduce the likelihood of progression to severe respiratory events.

Careful surveillance for infection should be performed for patients treated with terlipressin, and infection should be promptly treated. Consistent with the vasoconstrictive effect of terlipressin, ischemic events were observed in the clinical studies. These events are manageable with dose interruption or permanent discontinuation of terlipressin, if required.

Based on the data from the 3 placebo-controlled studies, there appears to be an upper limit of baseline SCr (approximately 5 mg/dL) above which there is a substantially reduced likelihood of achieving HRS-1 reversal. Additionally, a higher proportion of these subjects treated with terlipressin experienced severe and serious adverse events, and adverse events leading to death than those treated with placebo. Ninety-day mortality is higher for these subjects with the most advanced renal dysfunction treated with terlipressin than those treated with placebo. Thus, for patients with the most advanced renal failure and SCr $\geq$5 mg/dL, treatment with terlipressin is not recommended and initiating terlipressin therapy needs to be carefully considered with regard to potential benefits versus the known risks for this severely compromised population.

In summary, HRS-1 is a serious condition of reversible functional organ failure due to reduced blood flow to the kidney. If not reversed rapidly, the condition will progress to irreversible kidney damage and further worsen the patient's prognosis. The primary goals of treatment of HRS-1 are acute improvement in renal function and reversal of the functional renal failure.

Terlipressin is a short-term therapy that accomplishes these treatment goals by decreasing splanchnic vasodilation, thereby improving renal hemodynamics, ameliorating afferent renal vasoconstriction, and improving kidney function. The placebo-controlled studies consistently show improvements in SCr, a direct measure of renal function, and in important clinical outcomes, including reduced need for RRT, reduced ICU stay, and better outcomes (in terms of survival and RRT use) after liver transplantation. The risks of terlipressin are well characterized, predictable, recognizable, and generally manageable, particularly as terlipressin is used only in the hospital in patients who are already being monitored because of their decompensated liver disease.

There is a clear medical need to make this treatment available to improve the care of critically ill patients with HRS-1 in the US.

1.2 HRS-1: The Unmet Need

HRS-1 results from a complex interplay of pathophysiological processes, leading to either simultaneous or sequential organ dysfunctions in patients with decompensated cirrhosis.

There are approximately 650,000 patients with cirrhosis in the US (Scaglione 2017). About 60% of them will develop decompensated disease within 10 years of their initial diagnosis of cirrhosis. Decompensation means the appearance of complications that include ascites, hepatic encephalopathy, jaundice, and coagulopathy. Patients with decompensated cirrhosis are at risk of additional precipitating events that can lead to multiple organ failure, such as occurs in HRS-1.

Liver transplantation is the only definitive treatment for the advanced decompensated cirrhosis that underlies HRS-1; however, not all patients with decompensated cirrhosis, with or without HRS-1, are candidates for liver transplantation. HRS-1 is an orphan indication; it affects an estimated 35,000 patients in the US annually (Pant 2016). Based on United Network for Organ Sharing (UNOS) data, there were approximately 8,200 liver transplants performed in the US in 2019 (OPTN 2020). Hence, most HRS-1 patients are not liver transplant candidates or receive it in a timely manner. Challenges to patients in need of a liver transplant include the complex system for being listed for an organ transplant, the process of being prioritized for transplant and managed while on the waiting list, and availability of a donor organ (OPTN 2020).

HRS-1 is an acute complication of decompensated cirrhosis arising from hemodynamic changes that ultimately lead to functional renal failure from reduced blood supply to the kidney. The hemodynamic cascade includes the development of portal hypertension, consequent to liver structural changes due to advanced cirrhosis. The resulting shear stress on the blood vessels in the splanchnic bed causes production of local vasodilator substances and the splanchnic arterial vasodilation that is characteristic of HRS-1. These processes culminate in drastically reduced renal perfusion and functional renal failure.

HRS-1 involves multiple organ systems and occurs on a background of a high incidence of infection, sepsis, and other cirrhotic complications. It is typically precipitated by a reversible event such as bleeding, infection, or severe alcoholic hepatitis. Although HRS-1 is potentially reversible, the addition of renal failure to an already complicated clinical milieu can cause the patient's condition to deteriorate rapidly, requiring urgent care. See Section 2.1 for more discussion of HRS-1 pathophysiology.

HRS-1 is a diagnosis of exclusion, after structural renal diseases and pre-renal azotemia have been ruled out. According to the ICA diagnostic criteria for HRS-1, the disease is characterized by rapidly progressive renal failure. In 2007 it was defined by doubling of the initial SCr to >2.5 milligrams per deciliter (mg/dL) in <2 weeks (Salerno 2007).

The development of HRS-1 not only jeopardizes the patient's physical and emotional well-being, it also creates stress and fear for the family as they come to understand the risk for irreversible

comorbidities and death. For those already on the transplant waiting list, the development of HRS-1 may mean the patient becomes too ill to receive a liver transplant after having gone through the extensive work-up required for being listed. Patients who cannot be transplanted, and their families, will have to face the discussion of end-of-life issues. For the hospital team treating HRS-1 patients, it is a demanding process of urgent care coordinated across multiple specialties. At the same time, these patients add to the burden on the healthcare system, increasing utilization with prolonged hospital stays, increased ICU days, and high rate of re-admissions.

The immediate goal of HRS-1 treatment is to improve renal function and reverse the pathophysiology of HRS-1. For the majority of HRS-1 patients who are not candidates for liver transplant, reversing HRS-1 and restoring renal function facilitates medical management of their overall condition and reduces utilization of RRT. In patients who have a reversible component to the event that precipitated decompensation, improving renal function may provide the time needed for the underlying liver disease to improve (Wong 2015). This is the case in patients with acute alcoholic hepatitis, autoimmune hepatitis-related cirrhosis, EVH, and infection.

For patients who may be a candidate for liver transplantation, reversing HRS-1 is associated with better outcomes both pre- and post-transplant (Sanyal 2008, Gluud 2012, Hiremath 2013, Boyer 2016, Zheng 2017, Wang 2018). Pre-transplant renal function is the most important predictive factor for post-transplant renal function and post-transplant patient and graft survival (Nair 2002, Weismüller 2008, Watt 2010).

RRT is an effective measure for temporarily addressing the effects of renal failure, but it does not restore renal function or improve the prognosis of HRS-1 patients. Because of the poor overall condition of HRS-1 patients, including increased risk for major bleeding complications, RRT is a high-risk procedure in this setting.

Albumin and vasoconstrictor therapy are the mainstays of pharmacologic treatment for HRS-1. Albumin has a volume expanding effect, thereby improving effective arterial blood volume. It may also limit the extent of inflammation that accompanies acute decompensated cirrhosis.

Vasoconstrictors reduce the vasodilation central to HRS-1. There are several approaches to vasoconstrictor therapy for HRS-1, none of which is approved for use in the treatment of HRS-1 in the US. The combination of midodrine and octreotide is readily available and thus frequently used off-label in the US, despite limited evidence of efficacy in the literature (Cavallin 2015, Facciorusso 2017). Norepinephrine may be used to treat HRS-1 in the ICU setting, but, again, there are limited data supporting this practice (Zheng 2017, Arora 2020). Arginine-vasopressin is also available but is not recommended due to ischemic AEs.

Outside of North America, in much of the rest of the world, terlipressin is the vasoconstrictor of choice for HRS-1, due to its direct effect in reversing the fundamental hemodynamic pathophysiology of HRS-1.

1.3 Terlipressin for HRS-1

Together with albumin, terlipressin is the standard of care for HRS-1 (EASL 2018) in the United Kingdom, Germany, Australia, and other countries where it is available. The use of terlipressin with albumin is associated with improved renal function and better clinical outcomes in patients with HRS-1 compared with placebo, no intervention, or albumin alone (Sanyal 2008, Gluud 2012, Hiremath 2013, Boyer 2016, Zheng 2017, Wang 2018).

Terlipressin acts as a splanchnic and systemic vasoconstrictor via the vascular vasopressin V_1 receptors. This V_1 selectivity enables terlipressin to act directly on the splanchnic arterioles, reducing portal inflow and thereby reducing portal pressure. This has the effect of redistributing part of the splanchnic blood volume to the systemic circulation, improving the filling of the central circulation. In the systemic circulation, terlipressin reduces systemic vasodilation, thereby improving systemic arterial pressure and hence renal perfusion. See Sections 2.2 and 4.1 for more discussion of the rationale for terlipressin treatment of HRS-1 and its mechanism of action, respectively.

Terlipressin is administered by intravenous (IV) bolus in the hospital setting, with a treatment period of up to 14 days and an average duration of 6 days. Retreatment may be indicated if HRS-1 resolves and then recurs.

The original US New Drug Application (NDA) for terlipressin was submitted in 2009 based primarily on the OT-0401 study and published literature. The current resubmission includes the pivotal CONFIRM study conducted by Mallinckrodt and reflects the culmination of a sustained, 17-year effort in collaboration with the FDA to develop terlipressin for use in the US.

1.4 Efficacy

The totality of evidence from 3 randomized, placebo-controlled clinical studies demonstrates that acute treatment with terlipressin delivers consistent and clinically meaningful improvements in renal function and reverses HRS-1.

The pivotal CONFIRM study, which was the largest and most recent of the 3 studies, and the supportive OT-0401 study form the regulatory basis for approval for terlipressin. Additional efficacy data are provided by the REVERSE study, which demonstrated a clinically meaningful improvement in renal function when compared to placebo.

All 3 studies enrolled adult subjects with cirrhosis, ascites, and a diagnosis of HRS-1. The dosing regimens were similar, with all studies administering terlipressin 1 mg (with the ability to increase dose to 2 mg) or placebo IV every 6 hours (q6h). Subjects in both treatment groups received standard of care albumin therapy, per guideline recommendations. No other vasopressor agents were used during the study treatment periods.

1.4.1 Study Endpoints

The primary endpoints of the 3 studies focused on successful treatment of HRS-1; key differences were the result of learnings from each previous study, updates to treatment guidelines for the management of HRS-1, and input from the FDA.

OT-0401 (n=112) was the first study, conducted between 2004 to 2006. The primary endpoint was Treatment Success at Day 14, defined as the percentage of subjects alive with a reversal of HRS. Reversal was defined as SCr ≤1.5 mg/dL on 2 measurements obtained 48 hours apart, without dialysis or recurrence of HRS-1 (Table 1). In the original analysis of the primary endpoint, the incidence of Treatment Success in the terlipressin group was double that of placebo but did not achieve statistical significance. Logistical issues were identified in the data collection required for the primary endpoint: for example, the required SCr value at Day 14 was difficult to collect in subjects who were discharged prior to Day 14.

These issues were discussed with the FDA, and it was agreed to collect additional post-treatment SCr data from existing medical records for all subjects who met a predefined threshold of SCr improvement. The re-analysis showed that 2 additional terlipressin subjects and none receiving placebo had met the criteria for the primary endpoint of Treatment Success at Day 14. The re-analysis resulted in the study demonstrating statistical significance for the primary endpoint. The re-analysis was submitted with the original NDA in 2009. Upon review, the FDA acknowledged OT-0401 would be considered confirmatory evidence of efficacy in the presence of 1 additional positive study, which is now available in the form of the pivotal CONFIRM study.

The REVERSE study (n=196) was conducted from 2010 to 2013. Based on the experience with OT-0401, the primary endpoint of Confirmed HRS Reversal eliminated the Day-14 SCr requirement and retained the minimum 48-hour timing for the confirmatory second SCr measurement of ≤1.5 mg/dL (Table 1). A provision was added that, in case of hospital discharge or transplantation before 48 hours, the 2 confirmatory SCr values had to be at least 22 hours apart, and the period of time constituting “on treatment” was increased to a maximum of 24 hours after the last dose of study medication.

The pivotal CONFIRM study (n=300), conducted from 2016 to 2019, built on learnings from the first 2 studies. Verified HRS Reversal was selected as the primary endpoint in CONFIRM to ensure the validity of the first SCr value of ≤1.5 mg/dL (Table 1). As agreed with FDA under a SPA, Verified HRS Reversal incorporates a second consecutive SCr value of ≤1.5 mg/dL obtained at least 2 hours from the first value, while the subject was receiving study treatment and without intervening RRT, liver transplant, transjugular intrahepatic portosystemic shunt (TIPS), or open-label vasopressors. In order to achieve Verified HRS Reversal, subjects had to be alive without RRT for at least 10 days after reaching the second SCr value ≤1.5 mg/dL.

Table 1. Primary Efficacy Endpoints in the Phase 3 Studies of Terlipressin

CONFIRM	OT-0401	REVERSE
Incidence of Verified HRS Reversal: subjects with 2 consecutive SCr values ≤1.5 mg/dL at least 2 hours apart, on treatment[a] by Day 14 or discharge[b] Subjects had to be alive without RRT for at least 10 days after achieving the 2 consecutive SCr values of ≤1.5 mg/dL	Incidence of Treatment Success at Day 14: subjects alive with a reversal of HRS (SCr ≤1.5 mg/dL, with at least 2 measurements 48 ± 8 h apart), without dialysis or recurrence of HRS (SCr value at Day 14 had to be <2.5 mg/dL)	Incidence of Confirmed HRS Reversal: subjects with 2 SCr values of ≤1.5 mg/dL at least 48 hours apart, on treatment, and without intervening RRT or liver transplant

HRS, hepatorenal syndrome; RRT, renal replacement therapy; SCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic shunt.

a. On treatment defined as up to 24 hours after the final dose of study drug.

b. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use were excluded from primary endpoint analysis. 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 17 August 2018. SCr values were also included if obtained after the administration of a single dose of dobutamine.

1.4.2 CONFIRM Study

The pivotal CONFIRM study demonstrated the efficacy of terlipressin compared with placebo in subjects with HRS-1. The primary endpoint was negotiated and agreed upon with FDA, and the p-value was successfully met.

Subjects were randomized to receive terlipressin (n=199) or placebo (n=101). Prior to randomization, enrolled subjects underwent an albumin challenge. Only subjects who did not respond adequately were then randomized into the study. After the initial dosing of 1 mg IV q6h, plus albumin in both groups, the drug dose was increased to 2 mg IV q6h if SCr had decreased by <30% from the baseline value on Day 4. Treatment was stopped by day 4 if SCr was at or above the baseline value.

The recommended albumin dose was 1 g/kg to a maximum of 100 g on the first day of study treatment and 20-40 g/day thereafter, as clinically indicated. Prior to the start of study drug, the mean total albumin exposure was 335.0 g for the terlipressin group and 370.7 g for the placebo group.

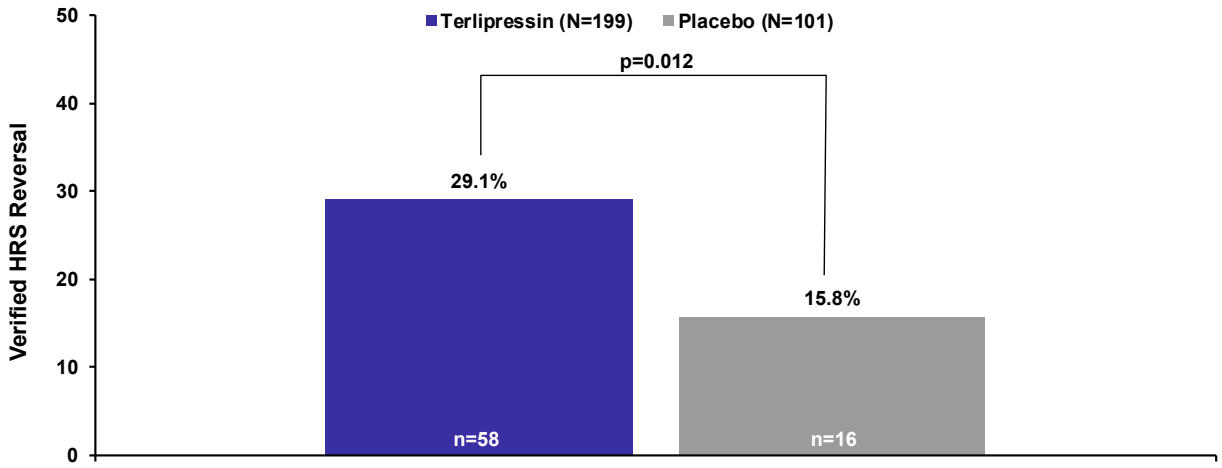
The treatment period was up to 14 days. More than two-thirds of the subjects did not increase dose at Day 4. The follow-up period was 90 days, with visits on Days 30, 60, and 90.

The CONFIRM patient population had HRS-1 and significantly progressed decompensated cirrhosis as indicated by an average baseline SCr of 3.5 mg/dL, average baseline Child-Pugh-Turcotte Score of 10, and average baseline Model for End Stage Liver Disease (MELD) score of 33. The MELD components include SCr, bilirubin, and international normalized ratio (INR). The

MELD score (ranging 6-40) assesses the degree of liver and kidney dysfunction in patients with cirrhosis; for example, a MELD of 33 represents severe dysfunction.

In CONFIRM, terlipressin demonstrated a significantly higher rate of Verified HRS Reversal compared with placebo (29.1% vs 15.8%, respectively, p=0.012) in this population of subjects with highly progressed cirrhosis with acute decompensation (Figure 1; also see Section 5.2.5.1,). There was no imputation for missing data and no missing data for the primary endpoint in CONFIRM.

Figure 1. Primary Endpoint of Verified HRS Reversal in the CONFIRM Study (ITT Population



The primary endpoint finding was supported by the 4 prespecified, alpha-protected secondary endpoint analyses. As shown in Table 2, terlipressin was significantly superior to placebo in HRS Reversal (defined as a SCr value of ≤1.5 mg/dL while receiving treatment by Day 14 or discharge); durability of HRS Reversal (defined as proportion of subjects with HRS Reversal without RRT at Day 30); and HRS Reversal in the high-risk systemic inflammatory response syndrome (SIRS) subgroup (Section 5.2.6.2). The incidence of Verified HRS Reversal without recurrence by Day 30 was 50% higher in the terlipressin group than in the placebo group, but this difference did not achieve statistical significance.

Table 2. Secondary Endpoint Results in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101	p-value[a]
HRS Reversal, n (%)	72 (36.2)	17 (16.8)	<0.001
95% CI	0.3, 0.4	0.1, 0.2	
Durability of HRS Reversal, n (%)	63 (31.7)	16 (15.8)	0.003
95% CI	0.3, 0.4	0.1, 0.2	
SIRS subgroup	N=84	N=48	
HRS Reversal, n (%)	28 (33.3)	3 (6.3)	<0.001
95% CI	0.2, 0.4	0.0, 0.1	
Verified HRS Reversal without HRS recurrence by Day 30, n (%)	N=199	N=101	
	48 (24.1)	16 (15.8)	0.092
95% CI	0.2, 0.3	0.1, 0.2	

CI, confidence interval; HRS, hepatorenal syndrome; ITT, intent-to-treat; LVP, large volume paracentesis; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; RRT, renal replacement therapy; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome; TIPS, transjugular intrahepatic portosystemic shunt.

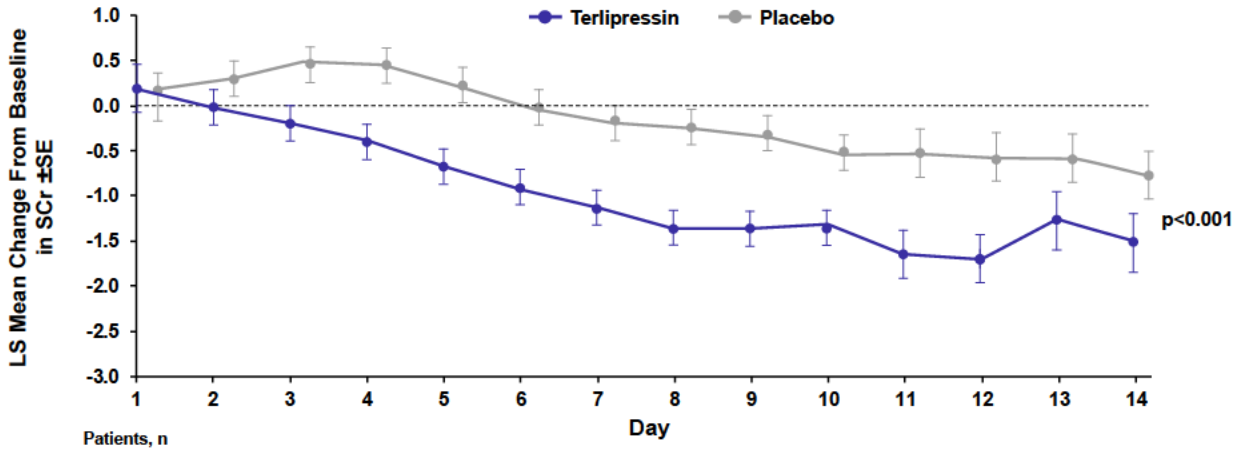
a. Cochran-Mantel-Haenszel Test stratified by qualifying SCr (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (≥1 event of ≥4 vs <4 L).

Note: The incidence of HRS Reversal: percentage of subjects with a SCr value ≤1.5 mg/dL while on treatment (on treatment defined as up to 24 hours after the final dose of study drug) by Day 14 or discharge. Durability of HRS Reversal: percentage of subjects with HRS Reversal (as defined above) without RRT to Day 30. Verified HRS Reversal without HRS recurrence by Day 30: percentage of subjects with verified HRS Reversal who did not experience a recurrence of HRS by Day 30. SCr values after RRT, TIPS placement, liver transplant, or open-label vasopressor treatment were excluded from these analyses.

Improvement in renal function, the most important goal of treatment in HRS-1 patients, was assessed by 4 additional prespecified endpoints: change in SCr from baseline to end of treatment (EOT); >30% improvement in SCr from baseline at EOT; change in creatinine clearance (CrCl) from baseline to EOT; and full and partial response to treatment based on the 2015 ICA guidelines (Angeli 2015a). Terlipressin treatment improved all measures compared with placebo (nominal p<0.001 for each).

As shown in Figure 2, terlipressin subjects had consistent improvements in renal function compared with placebo starting at Day 2 of the study through EOT. More than twice as many subjects receiving terlipressin achieved at least 30% improvement in renal function compared with those receiving placebo (Section 5.2.6.3).

Figure 2. Repeated Measures Analysis of Change from Baseline in SCr Level by Day in the CONFIRM Study (ITT Population)



ITT, intent-to-treat; LS, least squares; SCr, serum creatinine; SE, standard error.
p-value is nominal. No imputation methods were used for missing SCr values

In the setting of HRS-1, improvement in renal function should lead to reduction in the requirement for RRT, which is an invasive therapy that increases morbidity in patients with severely decompensated liver disease. In CONFIRM, consequent to improved renal function, there was a lower rate of RRT with terlipressin compared with placebo during the treatment period through Day 14 (Section 5.2.6.4.1), and a lower rate throughout the entire study period in subjects alive through Day 90. Time to first RRT was also greater in the terlipressin group compared with placebo subjects.

The incidence of RRT post-transplant was lower in terlipressin-treated subjects than in placebo-treated subjects, 19.6% vs 44.8%, respectively. The importance of this finding is not only the potential to reduce the burden and morbidity associated with RRT but also because the need for RRT post-transplant is predictive of poor graft function and survival (Nair 2002, Weismüller 2008, Watt 2010, Zand 2011).

Terlipressin treatment resulted in a shorter mean duration of ICU stay. In general, HRS-1 patients are expected to have a lengthy hospital stay due to the severity of the underlying decompensated cirrhosis and the additional functional renal failure, even if the HRS-1 is reversed by treatment. In CONFIRM, the mean total length of hospital stay and the percentage of subjects admitted to the ICU were similar in the 2 treatment groups. However, the mean length of stay in the ICU was 6.4 days in the terlipressin group compared with 13.5 days in the placebo group.

The results for the primary endpoint were consistent across key disease subgroups, with rates of Verified HRS Reversal 2 to 3 times greater in the terlipressin group compared with the placebo group for all assessments. These subgroups included 3 difficult-to-treat subgroups: those with

alcoholic hepatitis, SIRS, and low mean arterial pressure (MAP <70 mm Hg) at baseline. From a clinical perspective, patients with alcoholic hepatitis are especially important as they are often not initially considered candidates for liver transplant. By improving renal function and ameliorating portal hypertension-related inflammation, terlipressin treatment may allow these patients the time needed to recover from acute alcoholic hepatitis and acute decompensation. See Section 5.2.6 for more detail regarding CONFIRM efficacy.

1.4.3 Study OT-0401

In this study, 56 subjects with HRS-1 were randomized to terlipressin treatment and 56 to placebo. The initial results of the primary endpoint analysis of OT-0401 fell short of statistical significance. However, logistical issues that limited initial data collection for the Treatment Success at the Day 14 endpoint (described above) were identified and discussed with the FDA. This discussion led to an agreement to gather additional post-treatment SCr data from existing medical records from all subjects who had a SCr ≤1.7 mg/dL while on study treatment and to submit the re-analysis with the additional data during review of the original terlipressin NDA.

The results of the OT-0401 re-analysis provide further support for the efficacy findings of the pivotal CONFIRM study. In OT-0401, twice as many terlipressin subjects achieved Treatment Success at Day 14 compared with placebo, 28.6% vs 12.5% (p=0.037). The incidence of HRS Reversal in OT-0401 was higher in terlipressin-treated subjects compared with placebo-treated subjects: 33.9% vs 12.5% (nominal p=0.008). The terlipressin group also experienced a reduction in SCr from baseline to Day 14 relative to the placebo group. See Section 5.3.3 for more detail regarding OT-0401 efficacy.

1.4.4 REVERSE Study

The REVERSE study included 97 subjects with HRS-1 who were randomized to terlipressin treatment and 99 who received placebo. The study did not meet its prespecified endpoint but offered additional data on clinically meaningful improvement in renal function. For the primary endpoint, 50% more subjects receiving terlipressin achieved Confirmed HRS Reversal (defined in Table 1) than those receiving placebo, 19.6% vs 13.1%, respectively. For the prespecified endpoint of change from baseline to EOT in SCr, terlipressin demonstrated a 0.6 mg/dL greater reduction in SCr than placebo. All endpoints favored terlipressin and were directionally consistent with the other 2 studies, although the magnitude of some of the differences was smaller. See Section 5.4.3 for more detail regarding REVERSE efficacy.

1.4.5 Pooled Efficacy Analyses

Pooled analyses of the 3 phase 3 placebo-controlled studies provide further assessment of the efficacy and clinical impact of terlipressin in the treatment of HRS-1. The basis for pooling was that all 3 studies had a similar design, dosing regimen, and patient population. HRS Reversal, which was assessed in all of the studies, was chosen as the primary endpoint variable for the

pooled analyses. HRS Reversal is the standard endpoint in most published studies of HRS-1 and reflects the treatment goal in clinical practice and guidelines (EASL 2018).

In the prespecified pooled analysis, incidence of HRS Reversal was assessed in 3 key subgroups, identifiable at baseline: subjects with alcoholic hepatitis, SIRS, or low MAP (<70 mm Hg) at baseline. The likelihood of HRS Reversal was 3-7 times higher in the terlipressin group compared with the placebo group for all subgroups assessed, consistently higher than the overall population (Section 5.5.2).

Upon assessment of the incidence of HRS-1 reversal according to baseline SCr, it became apparent that there may be an upper limit for baseline SCr (approximately 5 mg/dL) above which there is a substantially reduced likelihood of achieving HRS-1 reversal.

Therefore, in an effort to optimize the benefit risk for patients who will be treated with terlipressin, we have evaluated the relationship of baseline SCr on HRS reversal and the benefits and risks of terlipressin in subgroups of subjects with a baseline of <5 mg/dL and ≥5 mg/dL. A SCr ≥ 5 mg/dL is the value used to define the highest grade of kidney failure within the Chronic Liver Failure-Sequential Organ Failure assessment (CLIF-SOFA) score.

The incidence of HRS-1 reversal is consistently higher with terlipressin compared with placebo in all baseline SCr sub-groups evaluated. However, in both treatment groups, subjects with a baseline SCr ≥5 g/dL have a lower incidence of HRS-1 reversal than subjects with a SCr <5 mg/dL. Specifically, in the sub-group of subjects with baseline SCr ≥5 mg/dL, the incidence of HRS-1 reversal is 9.1% in the terlipressin compared to 3.0% in the placebo group; these proportions are substantially lower than for subjects with a baseline SCr <5 mg/dL. The same pattern of results were seen in the pivotal CONFIRM study.

Identification of patients most likely to benefit from terlipressin treatment and how the benefit-risk of terlipressin can be optimized by assessment of baseline SCr is described in detail in Section 8.1.

Based on the FDA feedback during the pre-NDA meeting in October 2019 and subsequent communications, the Sponsor performed post-hoc analyses to understand trends in clinical benefit related to restoring renal function in transplanted subjects across the 3 studies. Liver transplant is the sole curative treatment for the underlying liver disease, but only approximately 25% of HRS-1 subjects received transplants in the terlipressin placebo-controlled clinical studies (Section 5.5.7.2). Improving clinical outcome in transplant patients is critically important, both for the individual patient and for graft survival in terms of effective allocation of donor livers.

The incidence of HRS Reversal in the pooled subgroup of transplanted subjects was more than double in terlipressin-treated subjects than in those receiving placebo. Consistent with the improvements in renal function, there were also reductions in the rates of RRT with terlipressin at each of the time points assessed.

Patients who require RRT after liver transplant are at an increased risk for graft dysfunction and death (Nair 2002, Weismüller 2008, Watt 2010). In the clinical trials, consistent with the impact of RRT on post-transplant survival, there were more transplanted subjects alive after 90 days in in the terlipressin group compared with the placebo group, 98.9% vs 91.0%, respectively.

Survival was not defined as a primary or secondary analysis in the CONFIRM trial. This clinical program cannot demonstrate a benefit in this population because survival is confounded by multiple co-morbidities in patients with HRS-1. Overall survival across the pooled phase 3 studies was similar between treatment groups. Refer to Section 6 for the Kaplan-Meyer curves and discussion. Terlipressin is an acute, short-term treatment for 1 complication of advanced progressive liver disease. Whereas terlipressin significantly improves renal function and reverses HRS-1, it does not treat the underlying decompensated cirrhosis or other organ dysfunctions and potential causes of mortality in these patients. In addition to HRS-1, patients frequently have concomitant conditions that include infection, sepsis, hepatic encephalopathy, coagulopathy, pulmonary dysfunction, and EVH.

1.4.6 Efficacy Conclusions

The results of the pivotal phase 3 CONFIRM study and the supportive phase 3 OT-0401 study show that terlipressin treatment is superior to placebo for achieving sustained reversal of HRS-1 and improved renal function. Terlipressin treatment is associated with additional clinical benefits, including decreased incidence of RRT and decreased length of ICU stay. Terlipressin significantly improves outcomes in liver transplant recipients. Finally, terlipressin is especially effective in the high-risk subgroups of subjects with alcoholic hepatitis, SIRS, and low MAP at baseline. Terlipressin treatment is not recommended for patients with the most advanced renal dysfunction (ie, baseline SCr greater than approximately 5 mg/dL) because of a reduced likelihood for HRS-1 reversal and increased potential for risks in these highly compromised patients. This, along with the rest of our proposed mitigation strategy, which will include tools available to the treating physician (eg, proposed labeling, increased education and awareness, and specialty distribution of the drug) should lead to a reduction in the key safety risks such as respiratory failure and early sepsis.

1.5 Safety

The safety profile of terlipressin is well characterized, with the majority of AEs being predictable, recognizable, and generally manageable in the hospital setting where HRS-1 patients are treated. Most of the events observed in the company-sponsored clinical studies were expected based on terlipressin's V_1-receptor activity and were consistent with the known experience with terlipressin outside the US.

The integrated phase 3 safety population comprises 349 subjects with HRS-1 who have received at least 1 dose of terlipressin in company-sponsored studies, including 200 subjects in CONFIRM, 56 subjects in OT-0401, and 93 subjects in REVERSE. These 349 subjects received

an average daily terlipressin dose of 3.6 mg for a mean duration of 6.2 days and a maximum duration of 25 days. Twelve subjects in the 3 studies were retreated after their initial treatment period (6 subjects in CONFIRM, 2 subjects in OT-0401, and 4 subjects in REVERSE). For these 12 subjects, the assessments of exposure and AEs combine the initial and retreatment periods.

There was a high incidence of AEs, SAEs, and mortality in both treatment groups. In the integrated safety population, the overall incidence of AEs was 91.1% in the terlipressin group and 90.4% in the placebo group. The incidence of SAEs was 65.0% in the terlipressin group and 59.8% in the placebo group. The incidence of treatment withdrawals due to AEs was 13.5% for subjects treated with terlipressin and 5.2% for those receiving placebo. Of the 13.5% of patients who discontinued in the terlipressin group, 4.6% were for gastrointestinal events, 3.7% were for ischemic events, 3.4% were for respiratory-related events, and 1.8% were for other events. Mortality up to 30 days after first treatment was 41.5% in the terlipressin group and 40.6% in the placebo group. See Section 7.2.7 for a tabular presentation of AEs.

The most commonly reported AEs leading to death within 30 days of treatment were as expected for this population with decompensated cirrhosis. In the terlipressin group, they were hepatic failure, including acute and chronic hepatic failure; respiratory failure, including acute respiratory failure; multiple organ dysfunction syndrome (MODS); and sepsis, including urosepsis and septic shock. The most common AE leading to death within 30 days with placebo was hepatic failure, including acute and chronic hepatic failure.

Overall, the reported AEs were similar in the 2 treatment groups. Adverse events reported with a >5% increased frequency with terlipressin were abdominal pain, diarrhea, dyspnea, and bradycardia. These events were generally mild to moderate and did not require dose interruption or discontinuation.

The reported SAEs was also similar between treatment groups. The most frequent SAEs for terlipressin were respiratory failure, MODS, chronic hepatic failure, hepatic failure, and sepsis. Ischemic SAEs were also more frequent with terlipressin than with placebo. The most common SAEs with placebo were hepatic failure and chronic hepatic failure. Respiratory failure was the only SAE reported at least 5% more frequently with terlipressin than placebo.

1.5.1 Safety in Subjects with the Most Advanced Renal Dysfunction

As described in Section 8.1, in an effort to optimize the benefit risk for patients who will be treated with terlipressin, we have evaluated the relationship of baseline SCr on the benefits and risks of terlipressin in subgroups of patients with a baseline SCr of <5 mg/dL and ≥5 mg/dL. The incidence of adverse events is high in both treatment groups in the pooled studies; 91.1% and 90.4% for terlipressin and placebo, respectively. However, when assessed by baseline SCr, the incidence of severe and serious adverse events, and adverse events leading to death is higher in the terlipressin group compared with placebo in the sub-group with baseline SCr value of ≥ 5.0 mg/dL. Importantly, the larger proportion of terlipressin-treated subjects with a fatal AE

through Day 30 appears to be driven by higher incidences in the terlipressin group of AEs known to associated with terlipressin treatment, including respiratory failure (Section 7.2.7.8.4), early septic shock (Section 7.2.7.8.5), and MODS (Section 7.2.7.8.6).

Identification of patients most likely to benefit from terlipressin treatment and how the benefit-risk of terlipressin can be optimized by assessment of baseline SCr is described in detail in Section 8.1.

1.5.2 Respiratory Events

In the integrated safety data, the incidence of SAEs of respiratory failure, including acute respiratory failure, was 11.2% with terlipressin and 4.4% with placebo. The mortality rate due to respiratory failure, including acute respiratory failure, was 7.7% with terlipressin vs 2.0% with placebo.

Patients with decompensated cirrhosis and HRS-1 frequently have underlying cardiopulmonary changes, including fluid overload, cirrhotic cardiomyopathy, intrapulmonary vascular shunting, and pulmonary mechanical effects of large volume ascites leading to pleural effusions, decreased intrathoracic volume, and atelectasis. These patients are also at increased risk of aspiration as a result of hepatic encephalopathy and upper GI bleeding. Terlipressin, by increasing cardiac afterload and effective circulating volume, particularly in the setting of albumin loading, may unmask or aggravate cardiac systolic and diastolic dysfunction or underlying respiratory issues. In addition, pre-existing respiratory disorders have been commonly reported in patients with decompensated cirrhosis. In this setting, the vasoactive effects of terlipressin may exacerbate perturbations of perfusion/ventilation relationships in the lung.

In aggregate, based on the cumulative data available, including detailed review of individual subjects, there appears to be an effect of terlipressin leading to respiratory-related AEs, including respiratory failure and acute respiratory failure. Subjects with more advanced liver disease, a significant history of prior or treatment-emergent cardiorespiratory events, recent upper GI hemorrhage, or increasing hepatic encephalopathy appeared to be more likely to develop respiratory failure or acute respiratory failure with terlipressin treatment. Terlipressin should be used with caution in these patients. The terlipressin dose should not be increased in patients with treatment-emergent cardiorespiratory events.

Section 8.2 provides a detailed discussion of the risk of respiratory failure in some patients treated with terlipressin, including identification of patients who may be a higher risk for such events and proposed actions for potentially mitigating this identified risk.

Patients with increasing dyspnea, cough, orthopnea, or tachypnea should be carefully evaluated for evidence of pulmonary edema. In patients with fluid overload, especially those with respiratory events (eg, dyspnea, respiratory distress), careful assessment of the volume of concomitant albumin and other fluids being administered should be undertaken; temporary

albumin dose reduction or discontinuation may be the most appropriate initial management. Judicious, short-term use of temporary diuretic therapy as per standard of care may be employed in some patients in whom a response to diuretic therapy is expected. If respiratory symptoms persist, further management should include dose reduction or temporary interruption of terlipressin dosing.

1.5.3 Sepsis and Septic Shock

In the integrated safety analysis, infection-related AEs were common in both treatment groups, with 26.1% of subjects on terlipressin and 21.3% of subjects on placebo reporting events. The incidence of sepsis, including events of septic shock and urosepsis, was higher in the terlipressin group compared with placebo, 9.7% vs 4.0%, respectively. A total of 5.7% of terlipressin-treated subjects and 1.6% of placebo-treated subjects died from sepsis, including events of septic shock and urosepsis.

The majority of sepsis and septic shock events in the terlipressin group occurred following the discontinuation of treatment, including about 40% that occurred more than 7 days after the last dose. These events can be identified as occurring early (end of treatment plus ≤7 days) and late (end of treatment plus ≥8 days). Detailed review of individual subjects with late sepsis indicated that they were unlikely to be related to terlipressin and more likely due to underlying decompensated cirrhosis.

Of the 24 terlipressin-treated subjects who experienced sepsis events within 7 days of the end of treatment, the majority developed sepsis following an event of respiratory failure or a clinically significant cardiorespiratory event, such as pulmonary edema, dyspnea, pleural effusion, and pneumonia. Of the remaining subjects, most had either an ongoing infection at baseline or developed an on-treatment infection during the study, including a urinary tract infection, a PICC line infection, and an intestinal obstruction, which are unlikely to be related to treatment with terlipressin.

Based on the cumulative data available, including detailed review of individual subjects, an association of terlipressin with a risk of developing sepsis/septic shock cannot be excluded. Sepsis may occur in association with or following cardiopulmonary events; more than half of the early cases of sepsis involved preceding cardiopulmonary events such as pneumonia, pulmonary edema, or pleural effusion. Sepsis may be mitigated in part by the same measures recommended above for respiratory failure. Section 8.2 provides a detailed discussion of the risk of respiratory failure and the related risk of sepsis in some patients treated with terlipressin, including identification of patients who may be a higher risk for such events and proposed actions for potentially mitigating these risks.

Careful surveillance for infection should be performed in patients receiving terlipressin and infection should be promptly treated.

1.5.4 Multiple Organ Dysfunction Syndrome

In the integrated analysis, the incidence of MODS through 7 days post-treatment was greater with terlipressin (5.4%) than with placebo (3.2%). Deaths due to MODS reported within 30 days post-treatment were 6.3% in terlipressin-treated subjects and 3.2% in placebo-treated subjects.

MODS events were evaluated over the course of the development program to better understand the apparent imbalance between terlipressin and placebo groups. Data from the REVERSE study showed that most of the affected patients had MODS at baseline, and it did not appear to worsen over the course of the study. In the subsequent CONFIRM study, the definition of an AE of MODS was clarified, and investigators were asked prospectively to also assess Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) scores and Acute-on-Chronic Liver Failure (ACLF) grades in all patients at baseline. These 2 scoring systems have been well validated in patients with decompensated cirrhosis and HRS-1. With a more rigorous, prespecified definition of MODS at baseline, the incidence of AEs of MODS in the CONFIRM study was similar between terlipressin- and placebo-treated subjects, 2.5% and 3.0%, respectively.

1.5.5 Ischemic Events

The vasoconstrictor effects of terlipressin are well described in the literature (Kiska-Kanowitz 2004, Narahara 2009, Krag 2010); ischemic events may include skin pallor/blanching, local skin necrosis, ischemic bowel, peripheral ischemia, and myocardial ischemia. In the integrated study population, 7.2% of subjects in the terlipressin group and 0.4% in the placebo group reported an ischemia-associated AE. The most common ischemia-associated AEs with terlipressin were skin discoloration, cyanosis, and intestinal ischemia. No case of skin necrosis was observed in any of the 3 studies in subjects receiving terlipressin. The incidence of withdrawal due to ischemia-related AEs were 3.7% in the terlipressin group compared with 0.4% in the placebo group.

Ischemia-related SAEs were more common in the terlipressin group, 2.9% compared with 0.4% of subjects in the placebo group. No ischemia-associated SAE occurred with a frequency difference of ≥2 percentage points between the treatment groups. No deaths due to ischemia-associated AEs were reported in the phase 3 studies.

The 7.2% incidence of ischemic AEs observed in the terlipressin group is similar to that reported in the literature, which ranges from 4-13% (Gluud 2012, Facciorusso 2017), and in the World Health Organization (WHO) global pharmacovigilance database. In general, ischemia-associated events are recognizable and manageable with dose interruption, followed by dose reduction or permanent discontinuation of drug, consistent with the warnings and precautions in the proposed terlipressin label.

1.5.6 Safety Conclusions

Adverse events associated with terlipressin are generally predictable, recognizable and manageable in the hospital setting where HRS-1 patients are treated.

As expected in this complex patient population, the incidence of AEs was high in both treatment groups. The type of events and their severity were consistent with the known safety profile of terlipressin and in subjects with underlying decompensated cirrhosis.

There was a higher incidence of respiratory failure on terlipressin; therefore, it should be used with caution in patients with a prior history of respiratory events or severe respiratory illness.

Patients receiving terlipressin should be carefully monitored for infection, and any infection observed should be treated promptly. Sepsis may occur in association with or following cardiopulmonary events and may be mitigated in part by the same measures recommended to address respiratory failure.

Consistent with the vasoconstrictive effect of terlipressin, ischemic events were observed. These are manageable with prompt treatment interruption and permanent discontinuation, if required. No fatal ischemic event was associated with terlipressin treatment.

Terlipressin treatment is not recommended for patients with the most advanced renal dysfunction (ie, baseline SCr greater than approximately 5 mg/dL) because of higher risk of adverse events with a lower likelihood of benefit in these highly compromised patients. This, along with the rest of our proposed mitigation strategy, which will include tools available to the treating physician (eg, proposed labeling, increased education and awareness, and specialty distribution of the drug) should lead to a reduction in the key safety risks such as respiratory failure and early sepsis.

Overall, the safety profile of terlipressin has been thoroughly characterized and supports the use of terlipressin in the acute treatment of patients with HRS-1.

1.6 Risk Mitigation and Optimizing the Benefit-Risk of Terlipressin

1.6.1 Baseline SCr

There appears to be an upper limit for baseline SCr (approximately 5 mg/dL) above which there is a substantially reduced likelihood of achieving HRS-1 reversal. Therefore, in an effort to optimize the benefit risk for patients who will be treated with terlipressin, we sought to evaluate the relationship of baseline SCr on HRS reversal and adverse events.

The incidence of HRS-1 reversal is consistently higher with terlipressin compared with placebo in all baseline SCr sub-groups evaluated. However, in both treatment groups, subjects with a baseline SCr ≥5 g/dL have a lower incidence of HRS-1 reversal than subjects with a SCr <5 mg/dL. Specifically, in the sub-group of subjects with baseline SCr ≥5 mg/dL, the incidence of HRS-1 reversal is 9.1% in the terlipressin compared to 3.0% in the placebo group; these

proportions are substantially lower than for subjects with a baseline SCr <5 mg/dL. The same results were seen in the pivotal CONFIRM study.

When assessed by baseline SCr, the incidence of severe and serious adverse events, and adverse events leading to death is higher in the terlipressin group compared to placebo in the sub-group with baseline SCr value of ≥ 5.0 mg/dL and a larger proportion of these terlipressin-treated subjects (65.9%) had a fatal AE through Day 30 than placebo-treated subjects (38.7%). Although the overall numbers of subjects in this sub-group are small, this difference between groups appears to be driven by higher incidences in the terlipressin group of fatal AEs of multi-organ dysfunction syndrome (11.4% versus 0% placebo), respiratory failure (4.5% versus 0% placebo), cardio-respiratory arrest (4.5% vs 0% placebo), and septic shock (4.5% vs. 0% placebo). Respiratory failure, early septic shock and, at least in part, MODS are associated with terlipressin therapy.

Finally, in subjects with a baseline SCr ≥5 mg/dL, 90-day mortality is higher for subjects in the terlipressin group than in the placebo group, in both the pooled data (Figure 3) and the pivotal CONFIRM study (Figure 4).

Figure 3: Overall Survival up to 90 Days by Treatment Group and Baseline SCr (Pooled Studies; Intent-to-treat Population)

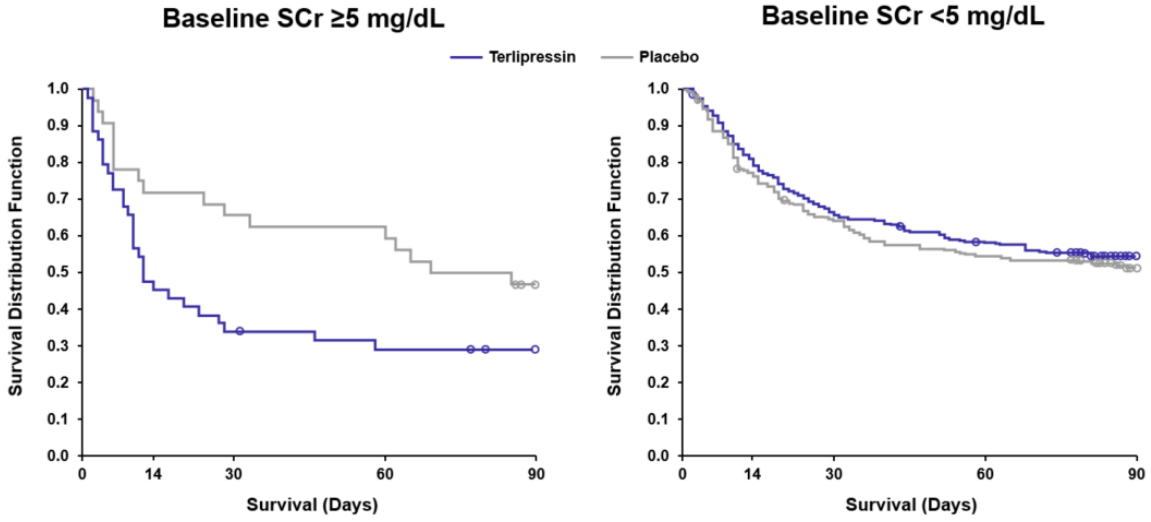
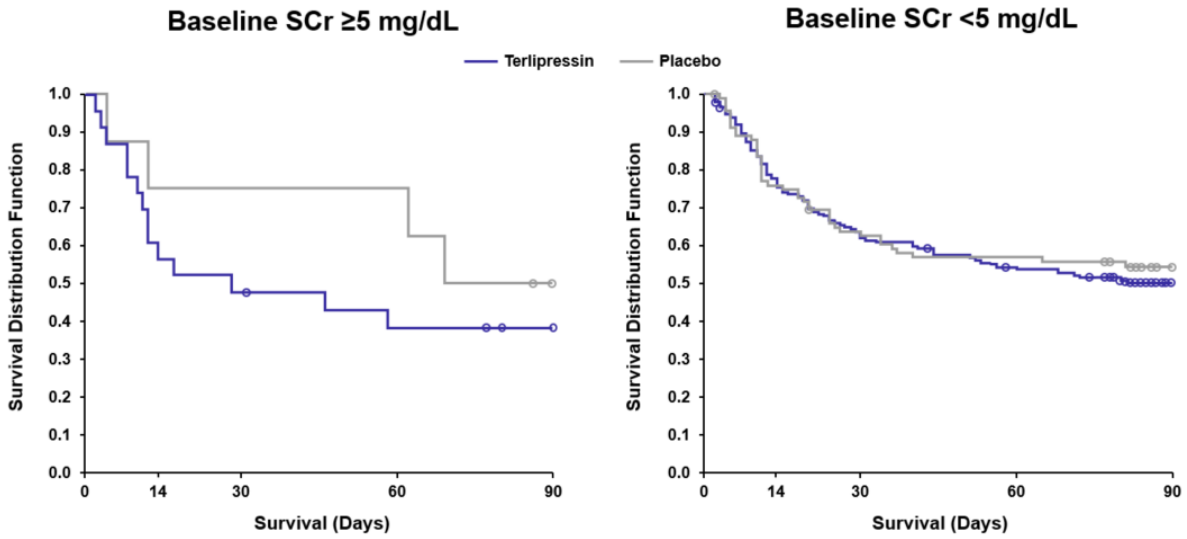


Figure 4: Overall Survival up to 90 Days by Treatment Group and Baseline SCr (CONFIRM; Intent-to-treat Population)



In conclusion, there appears to be an upper limit of baseline SCr (approximately 5 mg/dL) above which there is a substantially reduced likelihood of achieving HRS-1 reversal and subjects with a baseline SCr ≥5 mg/dL have a lower incidence of HRS-1 reversal versus subjects with serum creatinine values of <5 mg/dL regardless of treatment. However, a higher proportion of these subjects treated with terlipressin experienced severe and serious adverse events, and adverse events leading to death than those treated with placebo. Overall survival is also lower for these subjects with the most advanced renal dysfunction treated with terlipressin than those treated with placebo.

Thus, we believe that reducing exposure to terlipressin in patients with a baseline SCr ≥5 mg/dL improves the benefit-risk of terlipressin in a majority of patients. For patients with the most advanced renal failure and SCr ≥5 mg/dL, treatment with terlipressin is not recommended and initiating terlipressin therapy needs to be carefully considered with regard to potential benefits versus the known risks for this severely compromised population. The decision to use terlipressin in these patients can only be made on a case-by-case basis by the treating physician.

1.6.2 Respiratory Failure

Review of the terlipressin clinical database reveals an increased incidence in the proportion of subjects who experienced a serious adverse event of respiratory failure, including acute respiratory failure, in the terlipressin group, compared with the placebo group, during the clinical development program (11.2% vs. 4.4%, respectively). In addition, an increased incidence of

deaths due to respiratory failure is observed in the terlipressin group, compared with the placebo group (7.7% vs. 2.0%, respectively).

This imbalance was greatest in the most recent CONFIRM study where serious events of respiratory failure were reported for 14.0% of terlipressin-treated subjects and 5.1% of placebo-treated subjects; incidence of deaths due to respiratory failure up to 30 days post-treatment in CONFIRM was 8.5% and 1.0% in the 2 treatment groups, respectively. It is likely that the higher incidence of these events in CONFIRM when compared with OT-0401 and REVERSE was driven by a shift in clinical practice toward greater use of albumin over the course of the approximately15-year clinical development program, with the highest use observed during the CONFIRM study. The importance of this change in treatment guidelines regarding the use of albumin to treat HRS-1 and its potential association with increased incidences of respiratory events, including respiratory failure, is discussed in detail in Section 8.2.

Subjects with more advanced decompensated cirrhosis, a significant history of prior, baseline, or treatment-emergent events or features of respiratory issues (primarily dyspnea, hypotension, pleural effusion, cardiac murmur, hematemesis, wheezing, cardiomegaly, pneumonia/aspiration pneumonia, atelectasis, increasing hepatic encephalopathy, esophageal varices hemorrhage) or recent upper GI hemorrhage appear more likely to develop respiratory failure/acute respiratory failure with terlipressin treatment.

These data support the conclusion that dyspnea, hepatic encephalopathy, upper GI bleeding, atelectasis, and aspiration pneumonia, in the setting of hypervolemia and preexisting cardiovascular and respiratory disease, account for much of the increased incidence, and increased severity, of respiratory failure observed in terlipressin-treated subjects.

It is possible that the incidence of respiratory failure observed in the terlipressin clinical program could be favorably impacted by a mitigation strategy designed to reduce the proportions of patients who progress to respiratory failure. As the Sponsor has observed that events of sepsis may complicate events of respiratory failure or other pulmonary disorders, especially pneumonia, a mitigation strategy directed at decreasing the incidence of respiratory failure might also mitigate the risk for events of sepsis, including those leading to death. The reason for the association between respiratory disorders, especially respiratory failure, and sepsis is not clear. It may primarily be the result of the spread of bacteria from areas of pneumonia to the blood and other organs, although in some cases it could reflect the systemic effects of hypoxia and acidemia resulting from impaired gas exchange on the integrity of the intestinal mucosa and bacterial translocation into the blood.

We propose the following mitigation guidance to help identify those patients who may be at greater risk and to reduce the likelihood of progression to severe respiratory events, which may be complicated by associated events of sepsis and can lead to death:

- Patients with new onset or worsening dyspnea, tachypnea, or significant respiratory disease should be stabilized prior to receiving terlipressin. This includes managing fluid overload and pneumonia.
- Treatment with terlipressin is not recommended in patients with serum creatinine ≥ 5.0 mg/dL.
- Fluid overload should be managed by decreasing the administration of albumin and other fluids and judicious use of diuretics. If pneumonia occurs or progresses, or pulmonary edema is severe, terlipressin dosing should be interrupted, reduced, or discontinued.
- Patients with hepatic encephalopathy ≥3 are at increased risk for aspiration. Hepatic encephalopathy should be treated and the airway should be protected as clinically indicated prior to initiating terlipressin.

A retrospective analysis assessed the impact of our proposed mitigation strategy on respiratory events and their sequelae, by applying it to the clinical trial data to determine how much it might have reduced incidences of respiratory failure, sepsis, and death in subjects treated with terlipressin. This analysis shows that the mitigation strategy could potentially have decreased respiratory failure and acute respiratory failure events and deaths by more than 60% in terlipressin-treated subjects. Because of the association of sepsis events with respiratory failure or other pulmonary disorders, the mitigation strategy for respiratory failure could have also reduced the incidence of early sepsis (within 7 days of the end-of-treatment) by more than 50%. As about 60% of the events of sepsis occurred early in, during, or within 7 days of treatment, an overall decrease in sepsis events of about 30% might have been observed in the clinical program had the proposed mitigation strategy been incorporated at the time of the clinical trials.

When mortality through Day 90 was analyzed for the pooled safety population, after removing fatal events that would have been possibly mitigated by the proposed mitigation strategy, results show a potential, meaningful impact of the strategy on decreasing mortality in the terlipressin group. The incidence of deaths with this analysis was lower in the terlipressin group during the treatment period and at all subsequent time points through Day 90 (Table 66).

Details regarding this analysis and expected impact of the mitigation strategy are provide in Section 8.2.3.

We intend to further mitigate the potential risks of respiratory failure, which may be complicated by associated events of sepsis and can lead to death, by providing detailed product labeling that will inform healthcare providers of these potential risks in specific patient populations. In addition to labeling, we propose the implementation of a comprehensive education program in multiple formats for healthcare providers and institutions that are expected to be involved in the treatment of HRS-1 with terlipressin. The education program is proposed to include a communication to healthcare providers and institutions, highlighting the label recommendations

on appropriate patient selection and the risks associated with the use of terlipressin, including the risk of respiratory failure and associated risks of sepsis and death. We will evaluate the effectiveness of the education program on a regular basis and make adjustments as necessary.

Pharmacovigilance activities will involve monitoring events from the global safety database as well as enhanced pharmacovigilance activities for events of special interest and the use of a health care provider named-patient questionnaire. The questionnaire will be focused on the targeted, structured collection of additional data on the events of special interest associated with terlipressin following market authorization. Pharmacovigilance activities will also include periodic signal detection activities with a targeted focus to monitor known risks (eg, ischemic and respiratory events) and the evaluation of any potential new and evolving signals. Aggregate periodic safety reporting will be performed to confirm the safety profile and monitor the benefit-risk profile of terlipressin for injection.

1.7 Benefit-Risk

Terlipressin is an important acute therapy that addresses an urgent medical need among patients with advanced liver disease in the US. The efficacy and safety data support a favorable benefit-risk assessment for the treatment of HRS-1.

HRS-1 is a rare, acute, functional renal failure complicating decompensated cirrhosis. There is no approved or proven treatment for HRS-1 in the US. New treatments are needed to treat this orphan condition.

Terlipressin provides short-term in-hospital treatment to address the acute renal dysfunction associated with HRS-1. It is the only drug to have demonstrated a durable benefit in double-blind, randomized, placebo-controlled studies in patients with HRS-1 and is currently approved in 24 countries outside the US for the treatment of HRS-1. Terlipressin is recommended as first-line treatment in international treatment guidelines (eg, ICA 2015 and EASL 2018) for the treatment of HRS-1.

The main goals of treatment are acute improvement in renal function and reversal of the hemodynamic pathophysiology of HRS-1. Treatment with terlipressin accomplishes these goals by decreasing splanchnic vasodilation and thereby improving renal hemodynamics, ameliorating afferent renal vasoconstriction, and improving glomerular filtration rate (GFR). The placebo-controlled studies consistently show improvements in SCr, a direct measure of renal function. These translate to clinically meaningful improvements, including reduced RRT, shorter ICU stays, and better outcomes after liver transplantation.

1.7.1 Demonstrated Benefits

As demonstrated in the clinical studies, terlipressin improves renal function and reverses HRS-1 in the acute setting. These hemodynamic improvements translate to meaningful clinical benefits. There is a reduced incidence and frequency of RRT with terlipressin. This is particularly

important in vulnerable patients with decompensated cirrhosis who often have complications during and after dialysis, including a higher rate of bleeding events.

Reducing the incidence of RRT is also of benefit to the healthcare system. Overall, reversal of renal failure simplifies patient management, with less utilization of resources, such as shorter ICU stays (Allegretti 2018). In the pivotal CONFIRM study, the mean length of ICU stay for terlipressin-treated patients was less than half of that for placebo-treated patients, 6.4 vs 13.5 days, respectively.

In patients with a complex interplay of comorbidities, having one fewer complication is a valuable outcome. Restoring renal function also allows time to address other potentially reversible complications, such as alcoholic hepatitis (Wong 2015). Improving renal function pre-transplant results in better post-transplantation outcomes in patients who have a liver transplant (Nair 2002, Weismüller 2008, Watt 2010). By limiting use in patients with the most advanced renal failure (ie, baseline SCr ≥ 5 mg/dL) who have high 90-day mortality regardless of response to treatment, terlipressin, by virtue of restoring renal function and revering HRS, can lower short-term mortality in patients with HRS-1.

In both the CONFIRM study and the pooled efficacy analysis of the 3 phase 3 studies, terlipressin treatment was associated with improved clinical outcomes compared with placebo in the key subgroup of subjects who received liver transplants.

The benefit of terlipressin treatment was further analyzed in 3 important subgroups: subjects with alcoholic hepatitis, subjects with SIRS, and subjects with low MAP (<70 mm Hg) at baseline. There was a higher incidence of HRS-1 reversal with terlipressin treatment in all 3 of these difficult-to-treat subgroups compared with placebo. Subjects in these subgroups also had lower incidence of RRT with terlipressin.

1.7.2 Demonstrated Risks

Terlipressin has a well-established safety profile from clinical studies and >30 years of post-marketing experience. Adverse events experienced by patients treated with terlipressin are predictable, recognizable, and generally manageable by symptomatic treatment or by reducing or stopping terlipressin administration.

Ischemic events are an expected risk for terlipressin-treated patients. These events are consistent with the vasoconstrictive mechanism of action of terlipressin. In the clinical studies, all ischemic events were nonfatal and manageable with temporary interruption or discontinuation of terlipressin treatment, if needed. Terlipressin should be used with caution in patients with a history of ischemic events.

Gastrointestinal AEs, including abdominal pain, vomiting, and diarrhea, were the most frequently occurring AEs reported by terlipressin-treated subjects across the 3 studies. Abdominal pain reflects the effect of V_1 receptor activation in the gut leading to increased

peristalsis. It is generally cramping in nature and is rarely associated with ischemia. GI events are generally manageable symptomatically or with dose reduction.

Respiratory disorders are frequently seen in patients with decompensated cirrhosis and constitute a known risk associated with the use of terlipressin. In the clinical studies, there was a higher risk of respiratory failure in patients with more advanced disease, a history of or treatment-emergent cardiorespiratory events, recent upper GI hemorrhage, or increasing hepatic encephalopathy. Terlipressin should be used with caution in these patients.

There was a higher incidence of sepsis and septic shock with terlipressin compared with placebo. Sepsis, septic shock, and other bacterial infections are common complications of decompensated cirrhosis, and septic shock is a frequent cause of death in patients with cirrhosis and decompensated cirrhosis, including those with HRS-1. The majority of sepsis/septic shock events in the terlipressin group occurred after treatment, most often after ≥8 days. An effect of terlipressin associated with a risk of developing sepsis/septic shock in some patients cannot be excluded.

Terlipressin is not recommended for patients with the most advanced renal dysfunction (ie, baseline SCr ≥ 5 mg/dL). There is a lowered likelihood of HRS-1 reversal with terlipressin in these highly compromised patients and a higher incidence of severe, serious, and/or fatal AEs.

A detailed discussion of how those patients most likely to benefit from terlipressin treatment can be identified and how these risks can be mitigated in the appropriate patients is provided in Section 8.

1.7.3 Quantitative Benefit-Risk Evaluation

In deciding treatment for the individual HRS-1 patient, the overall benefit-risk profile of terlipressin must be considered in terms of the likelihood of benefit versus the potential for harm. Based on placebo-corrected numbers from the clinical trials, it is possible to predict how many patients treated with terlipressin would benefit over albumin alone, and weigh these against the potential serious harms (ie, SAEs) terlipressin could cause over albumin alone. The benefits are clear in terms of HRS reversal and improved kidney function, as reflected in lower SCr and reduced need for RRT, including reduced RRT use post-transplant (Table 3).

Because of the serious nature of respiratory failure and sepsis, it is also important to consider the impact of risk mitigation strategies in making an evidence-based decision for an individual patient. Based on the review of clinical trial data, applying the mitigation strategy described in Section 9 would potentially reduce the number of serious respiratory failure events by more than 60%, and the number of serious sepsis events by approximately 30%. This would have a favorable impact on the NNT analyses for respiratory failure and early sepsis events as indicated in Table 4. By incorporating the recommendation against use in the population of patients with a baseline SCr ≥5 mg/dL, this not only improves the survival estimate as shown in Section 8.1.2.1,

but it also results in lower NNTs for avoidance of RRT, also reflected in Table 4. While this is an important recommendation for optimizing the overall benefit/risk ratio, it is imperative that the treating physician have the ability to make this choice for each patient, based on access to approved and effective treatment and on individual benefits and risks.

Table 3: Number Needed to Treat (NNT) for Benefits and Harms of Terlipressin Treatment; Integrated Studies (Intent-to-treat Population)

NNT for Benefit		NNT for Harm	
HRS Reversal	6	Ischemic SAE[c]	89
No RRT by Day 30[a]	17	Respiratory failure SAE[c]	13
No RRT post-transplant[a,b]	22	Sepsis SAE ≤7 days post-treatment[c]	20

HRS, hepatorenal syndrome; ITT, intention-to-treat population; NNT, number needed to treat; RRT, renal replacement therapy; SAE, serious adverse event

a: For "No RRT by Day 30," REVERSE only captures yes/no if there was an RRT by these follow-up days. This information is used since there are no RRT dates for the time periods. For "No RRT post-transplant," if a subject is retreated, RRT can occur during the initial or retreatment period. Additionally, for REVERSE, if RRT is during the follow-up period, then it is captured as yes/no for day 30, 60, and 90 visit. In these cases, RRT date is assigned as the last visit date +1.

b: Subset of subjects receiving a transplant of the ITT population.

c: Initial and retreatment periods are combined for AEs.

Table 4: Number Needed to Treat (NNT) for Benefits and Harms of Terlipressin Treatment Applying Mitigation Strategy; Integrated Studies (Intent-to-treat Population)

NNT for Benefit		NNT for Harm	
HRS Reversal	6	Ischemic SAE[c]	71
No RRT by Day 30[a]	14	Respiratory failure SAE[c]	64
No RRT post-transplant[a,b]	19	Sepsis SAE ≤7 days post-treatment[c]	39

HRS, hepatorenal syndrome; ITT, intention-to-treat population; NNT, number needed to treat; RRT, renal replacement therapy; SAE, serious adverse event

a: For "No RRT by Day 30," REVERSE only captures yes/no if there was an RRT by these follow-up days. This information is used since there are no RRT dates for the time periods. For "No RRT post-transplant," if a subject is retreated, RRT can occur during the initial or retreatment period. Additionally, for REVERSE, if RRT is during the follow-up period, then it is captured as yes/no for day 30, 60, and 90 visit. In these cases, RRT date is assigned as the last visit date +1.

b: Subset of subjects receiving a transplant of the ITT population.

c: Initial and retreatment periods are combined for AEs.

1.7.4 Benefit-Risk Conclusions

The overall benefit-risk profile of terlipressin as an acute therapy for HRS-1 is favorable.

HRS-1 is an acute functional renal failure in patients already seriously ill with decompensated cirrhosis. If not reversed rapidly, this severe complication will progress to permanent renal failure on top of the existing advanced liver disease.

Terlipressin is a short-term therapy that improves renal function and reverses HRS-1. The benefits of terlipressin treatment, including improvement in RRT, reduction in ICU stay, and post-transplant survival are durable and clinically meaningful. The risks are well characterized, predictable, recognizable, and generally manageable, particularly as terlipressin is used only in-hospital in patients who are already closely monitored because of their decompensated liver disease. The proposed respiratory failure mitigation strategy combined with the recommendation not to treat patients with a baseline SCr ≥5 mg/dL will likely further enhance the favorable benefit-risk profile of terlipressin. The respiratory failure mitigation should reduce events of respiratory failure and early sepsis and associated mortality. The serum creatinine recommendation should further reduce fatal events and increase the proportion of patients avoiding RRT.

Terlipressin is the standard of care for HRS-1 in all of the countries where it is approved. It has been used successfully in Europe and elsewhere for >10 years for the treatment of HRS-1. Until now, sufficient clinical study data were not available to support approval in the US. With the recently completed CONFIRM study, there is compelling evidence for terlipressin use.

US patients with HRS-1 deserve access to this important medication. The majority of patients who develop HRS-1 in the US do not receive a liver transplant and have no viable, effective, FDA approved, and proven treatment option. There is a clear medical need to make terlipressin available to improve care for these vulnerable patients.

2 TERLIPRESSIN RATIONALE AND DEVELOPMENTAL HISTORY

HRS-1 is a rare, acute, serious condition for which there is no approved pharmacologic treatment in the US. To meet this medical need, Mallinckrodt has developed terlipressin for injection for the indication of "the treatment of adults with hepatorenal syndrome type 1."

The complex pathophysiology and hemodynamic changes characteristic of HRS-1 are discussed below, along with the properties of terlipressin that directly address these changes.

Mallinckrodt has worked closely with the FDA to ensure that regulatory requirements have been met for the terlipressin clinical development program. The regulatory history of terlipressin is summarized in Section 2.4.

2.1 Pathophysiology of HRS-1

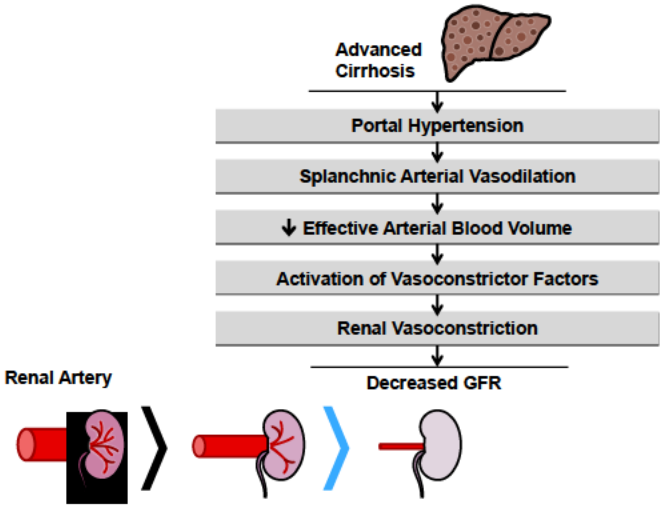
HRS-1 is a serious complication of advanced cirrhosis resulting from a complex interplay of pathophysiological processes, leading to either simultaneous or sequential organ dysfunctions in patients with decompensated cirrhosis.

An estimated 650,000 patients in the US have cirrhosis. Approximately 60% of them develop decompensation within 10 years of the initial diagnosis. Decompensation is characterized by the appearance of complications such as variceal hemorrhage, ascites, hepatic encephalopathy, jaundice, and coagulopathy. Decompensation occurs in the setting of chronic liver disease and can be induced by reversible conditions such as alcoholic hepatitis or through progressive hepatic failure, which leaves the patient with little remaining hepatic reserve. Patients with decompensated cirrhosis are at continued risk of additional precipitating events, including infection, alcoholic hepatitis, drug-induced liver injury, or GI bleed. These events can lead to acute life-threatening complications, such as the functional renal failure that occurs with HRS-1.

The development of HRS-1 is a crisis for patients with decompensated cirrhosis, making them among the most challenging of all patients with liver disease to treat. Patients require urgent care in a clinical setting that involves competing comorbidities and causes of mortality. The complex pathophysiology of HRS-1 involves the liver, kidneys, heart, endocrine, and nervous system and takes place on a background of high risk for infection, sepsis, and additional complications of cirrhosis, such as variceal bleeding.

The progression of hemodynamic changes involved in HRS-1 is shown in Figure 5. Although potentially reversible, the addition of renal failure to this clinical milieu can cause the patient's condition to decline rapidly.

Figure 5. Pathophysiologic Progression of HRS-1



Cirrhosis is associated with a number of circulatory changes (Wong 2012). These may include distortion of liver architecture, with obstruction to portal flow, leading to the development of sinusoidal portal hypertension. The consequent increased shear stress on the splanchnic vessels due to splanchnic outflow obstruction causes increased production of local vasodilator substances in the splanchnic bed, producing splanchnic arterial vasodilation. These local vasodilator substances may enter the systemic circulation through portal hypertension-related portosystemic shunts. Systemic arterial vasodilation results, with a consequent reduction in total systemic vascular resistance. There is a reduction in the effective arterial blood volume, which manifests as systemic hypotension.

Several homeostatic mechanisms are recruited to counteract the reduced arterial pressure—including activation of vasoconstrictor systems. Activation of the vasoconstrictor systems seeks to decrease the expanded vascular capacitance, while directing the kidneys to retain sodium. Increases in heart rate and left ejection fraction seek to maintain hemodynamic homeostasis. Nonosmotic activation of endogenous vasopressin causes water retention, which in turn expands extracellular fluid volume. In the presence of portal hypertension, the excess volume is preferentially localized in the peritoneal cavity as ascites.

As cirrhosis advances, splanchnic vasodilation increases. This leads to further abnormalities in the systemic circulation, with greater reduction in effective arterial blood volume and consequent greater activation of vasoconstrictor systems, causing renal blood flow and GFR to decline. Ultimately, the ongoing cycle of pathophysiological processes leads to HRS-1, which is a functional renal failure of circulatory origin in the absence of underlying kidney pathology.

2.2 Treatment of HRS-1

The goal of HRS-1 treatment is rapid improvement in renal function and reversal of the pathophysiology of HRS-1. For the majority of HRS-1 patients who are not candidates for liver transplant, reversing HRS-1 and improving renal function facilitates medical management of their overall condition. In patients who have a reversible component to the event that precipitated decompensation, improving renal function may provide the time needed for the underlying liver disease to improve (Wong 2015). This is the case in patients with acute alcoholic hepatitis, autoimmune hepatitis-related cirrhosis, EVH, and infection.

For patients who may be candidates for liver transplantation, reversing HRS-1 is associated with better outcomes both pre- and post-transplant (Sanyal 2008, Gluud 2012, Hiremath 2013, Boyer 2016, Zheng 2017, Wang 2018). Pre-transplant renal function is the most important predictive factor of post-transplant renal function and post-transplant patient and graft survival (Nair 2002, Weismüller 2008, Watt 2010).

Nonpharmacologic care for patients with renal failure often includes RRT. RRT is an effective measure for temporarily addressing the effects of renal failure, but it does not restore renal function or improve the prognosis of HRS-1 patients. Because of the poor overall condition of HRS-1 patients, including increased risk for major bleeding complications, RRT is a high-risk procedure in this setting.

Increased understanding of the pathophysiology of HRS-1 supports the beneficial role of vasoconstrictive drug therapy in this hyperdynamic circulatory setting (Salerno 2007, Ginès 2009, EASL 2018). Vasoconstrictor drugs correct the splanchnic and systemic vasodilation associated with HRS-1 and have been shown to improve renal hemodynamics, ameliorate afferent renal vasoconstriction, and improve GFR. Vasoconstrictor therapy is typically administered with albumin, which has a volume expanding effect, thereby improving the effective arterial blood volume. Albumin can also dampen the extent of inflammation in these patients.

There are several approaches to vasoconstrictor therapy for HRS-1, none of which is approved for marketing in the US. The combination of midodrine and octreotide is readily available and thus frequently used outside of labeling in the US, despite limited evidence of efficacy in the literature (Cavallin 2015, Facciorusso 2017). Norepinephrine may be used to treat HRS-1 in the ICU setting, but, again, there are limited data supporting this practice (Zheng 2017, Arora 2020). Arginine-vasopressin is also available but not recommended due to safety concerns.

In most of the world outside of North America, terlipressin is the vasoconstrictor of choice for HRS-1, due to its direct effect in reversing the fundamental hemodynamic pathophysiology of HRS-1 (Angeli 2015a, EASL 2018).

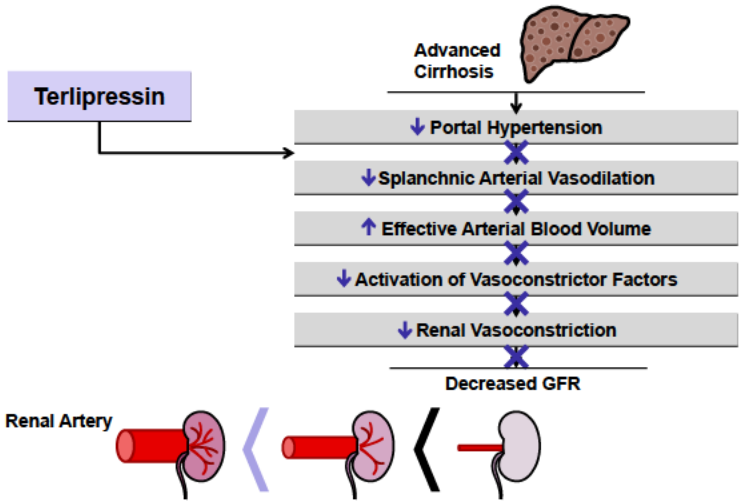
2.3 Terlipressin for HRS-1

Terlipressin is a synthetic vasopressin analogue that is a prodrug for lysine-vasopressin. The formation of lysine-vasopressin from terlipressin involves sequential cleavage by tissue peptidases, so that lysine-vasopressin is slowly released into the systemic circulation. The slower onset and more sustained vasoconstrictor effect of terlipressin represents a clinical advantage over arginine-vasopressin, which has a rapid onset, a narrow therapeutic index, and is associated with significant ischemic AEs. The half-life of terlipressin is 50 minutes, and the half-life of the active moiety, lysine-vasopressin, is 3 hours

Terlipressin is administered intravenously with a typical treatment period of 6 days, but patients can be treated for up to 14 days, if needed. If the patient's underlying condition is not resolved and there is another precipitating event resulting in HRS-1, the patient may be retreated with terlipressin.

Terlipressin reverses the hemodynamic abnormalities responsible for HRS-1 (Figure 6). It acts via the vascular vasopressin V_1 receptors. At the dose of terlipressin used to treat HRS-1 patients, the strong V_1-mediated vasoconstrictor activity is the pharmacodynamic mechanism responsible for its clinical activity.

Figure 6. Direct Effect of Terlipressin on Hemodynamic Components of HRS 1



In the splanchnic vascular bed, V_1 receptor activation selectively enables terlipressin to act directly on the splanchnic arterioles, reducing portal inflow and portal pressure. This also has the effect of redistributing the splanchnic blood volume to the systemic circulation, improving the filling of the central circulation. In the systemic circulation, terlipressin has the effect of reducing

the extent of the systemic vasodilation, thereby improving the systemic pressure and hence the renal perfusion pressure. These direct effects of terlipressin on the vasculature overcome the hemodynamic disruptions of HRS-1, reversing renal vasoconstriction, restoring renal perfusion, and increasing GFR (Arroyo 2000, Ginès 2003, Kiszka-Kanowitz 2004).

In addition, preliminary data suggest that terlipressin may have a suppressive effect on circulating levels of proinflammatory cytokines that play an important role in the development of HRS-1 (Moreau 2002, Zhao 2004, EASL 2018). Terlipressin may also improve renal function in HRS-1 via this mechanism, independent from its hemodynamic effect (Wong 2017).

A recent meta-analysis of 13 randomized, controlled studies enrolling a total of 739 patients with HRS-1 evaluated terlipressin and 2 other modes of vasoconstrictor therapy used in this setting, norepinephrine and the combination of midodrine and octreotide (Facciorusso 2017). Terlipressin was superior to placebo in reversal of HRS in all 5 of the randomized, placebo-controlled studies that were assessed. Neither of the other 2 therapies were compared to placebo for reversal of HRS. Only 1 randomized, controlled study with a total of 49 patients has been conducted with midodrine and octreotide (Cavallin 2015). This study used terlipressin as the comparator. HRS Reversal was achieved in 4.8% of patients treated with midodrine and octreotide compared with 55.5% of patients treated with terlipressin.

The meta-analysis also included 4 randomized, controlled studies comparing terlipressin and norepinephrine. For reversal of HRS, no difference was observed between terlipressin and norepinephrine (Facciorusso 2017). Subsequent to the meta-analysis, the largest study to date comparing norepinephrine to terlipressin was published recently (Arora 2020). It found HRS Reversal in 16.7% of the 60 patients treated with norepinephrine compared with 40% of the 60 patients treated with terlipressin. These data indicate efficacy with norepinephrine for the reversal of HRS-1, but the evidence is not robust. With the restriction that norepinephrine can only be administered in the ICU, it is not an optimal treatment option for HRS-1 patients.

There is an unmet medical need in the US to achieve the treatment goals of improving renal function and reversing HRS-1. Randomized, placebo-controlled clinical studies, clinical experience, and literature demonstrate the efficacy and safety of terlipressin in the acute treatment of HRS-1. With the successful completion of the CONFIRM study, there is now the high level of evidence needed to support the use of terlipressin in the treatment of HRS-1 in the US.

2.4 Regulatory History of Terlipressin

Mallinckrodt has worked closely with the FDA to ensure that regulatory requirements for approval in the US would be met by the terlipressin clinical development program. Mallinckrodt is the third sponsor to support the development of terlipressin, which began in 2003 and progressed through a complete response that the CONFIRM study satisfies, meeting the requirements for approval.

2.4.1 Orphan Therapeutics (2003 to 2010)

The initial US clinical development program for terlipressin comprised a single, well-controlled pivotal study, OT-0401, sponsored by Orphan Therapeutics, along with supportive published literature and data from the WHO safety database. Given the rare and life-threatening nature of this condition and the unmet medical need, the FDA granted Orphan Drug Designation and Fast-Track Designation for terlipressin use in HRS-1.

The primary endpoint in OT-0401 was Treatment Success at Day 14 (Table 1); in the original analysis the incidence in the terlipressin group was double that in the placebo group but did not attain statistical significance. There were logistical issues in collecting data as required for the primary endpoint that reduced the study's ability to demonstrate statistical significance. The main challenge was that the requirement for a SCr value on Day 14 was difficult to collect in subjects discharged prior to Day 14. In addition, in subjects who only responded with a first SCr value of ≤1.5 on Day 13 or 14, collection of the required second SCr value fell outside of the assessment window, causing the subjects to be considered nonresponders.

These issues were discussed with the FDA during the NDA review at a meeting in September 2009. It was agreed that additional post-treatment SCr data could be collected from the existing medical records of all study subjects who met a threshold for SCr improvement, regardless of treatment assignment, and the endpoint could be re-analyzed. An addendum to the OT-0401 study report provided the results of the re-analysis of the Treatment Success at Day 14 primary endpoint.

The re-analysis showed that 2 additional terlipressin subjects and none on placebo had additional SCr data that met the criteria for Treatment Success, so that the number of subjects meeting the requirement increased from 14/56 to 16/56. With the agreed-upon re-analysis, the OT-0401 study met its primary endpoint with a significantly higher rate of Treatment Success at Day 14 of 28.6% in the terlipressin group compared to 12.5% in the placebo group ($p=0.037$).

The FDA completed the NDA review in November 2009 and issued a Complete Response Letter (CRL) noting that the OT-0401 re-analysis was favorable but not sufficient to support approval based upon a single study. FDA advised that an additional adequate and well-controlled study would be needed to support approval. That study would need to be successful, using prespecified endpoint(s) and analytic plan, at $p<0.05$.

2.4.2 Ikaria Therapeutics (2010 to 2015)

In March 2010, Orphan Therapeutics licensed the NDA and its development rights for terlipressin in North America to Ikaria Therapeutics. Ikaria conducted REVERSE, a randomized, double-blind, placebo-controlled phase 3 study that completed on 10 May 2013. Ikaria submitted a request for a pre-submission meeting with FDA to discuss the REVERSE results and obtain guidance for the resubmission. REVERSE did not meet the prespecified primary endpoint, but

Ikaria considered the study to have shown a clinically meaningful improvement in SCr. In the pre-submission meeting, the FDA agreed that both OT-0401 and REVERSE were adequate and well-controlled studies and that the regulations at that time allowed for flexibility and scientific judgement when applying the standard of "substantial evidence of effectiveness" in assessing the totality of the evidence for approval. However, the FDA questioned whether the efficacy data were sufficient, given that REVERSE did not achieve the prespecified primary endpoint, and suggested another study may be needed. Ikaria decided to proceed and submitted a class 2 NDA resubmission in April 2015. In May 2015, the FDA issued an Incomplete Response Letter indicating that the resubmission was not a complete response because the prespecified endpoint of Confirmed HRS Reversal had not been met in the REVERSE study. However, the FDA re-affirmed that the OT-0401 study could be used as evidence to support an additional adequate and well-controlled study.

2.4.3 Mallinckrodt Pharmaceuticals (2015 to Present)

In 2015, Mallinckrodt acquired Ikaria Therapeutics and obtained ownership of the NDA. Through a SPA process, Mallinckrodt and the FDA reached agreement on the protocol for the CONFIRM study to ensure the design and study objectives would be sufficient to support the NDA resubmission. The FDA Guidance for Industry, Special Protocol Assessment (FDA 2018), explains that a SPA agreement "indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design (eg, entry criteria, dose selection, endpoints, and planned analyses). These elements are critical to ensuring that the study conducted under the protocol can be considered an adequate and well-controlled study that can support marketing approval (FDA 2018)." However, the existence of a SPA agreement does not guarantee that FDA will accept an NDA or that the study results will support approval. CONFIRM was completed in July 2019 and serves as the primary evidence for efficacy and safety of terlipressin in subjects with HRS-1 for the current NDA resubmission. Consistent with FDA's recommendations, CONFIRM is the pivotal study for the submission, and OT-0401 provides supportive evidence of efficacy. On 09 April 2020, FDA advised that the NDA resubmission with the CONFIRM results was accepted and considered a complete response to the 2009 CRL.

2.5 Clinical Development Program

The safety and efficacy of terlipressin is based primarily on the results of CONFIRM, with supportive evidence from OT-0401 and additional data from REVERSE. All 3 studies were randomized, double-blind, multicenter, placebo-controlled studies of the safety and efficacy of IV terlipressin in subjects with HRS-1. Together, they provide data for 352 subjects treated with terlipressin. All of the studies contributed safety data for the integrated analysis of safety. For the efficacy assessment, the studies all had primary endpoints assessing HRS Reversal although the specific endpoint definitions varied as did their results.

- CONFIRM (199 subjects treated with terlipressin; 101 subjects treated with placebo) achieved its primary endpoint of incidence of Verified HRS Reversal (Table 1), defined as the percentage of subjects with 2 consecutive SCr values ≤1.5 mg/dL at least 2 hours apart, while receiving treatment by Day 14 or discharge. Additionally, subjects had to be alive and without RRT for at least 10 days after reaching the second SCr value ≤1.5 mg/dL in order to achieve the primary endpoint.
- OT-0401 (56 subjects treated with terlipressin; 56 subjects treated with placebo) did not achieve its primary endpoint of Treatment Success at Day 14 (Table 1) in the prespecified analysis. A statistically significant difference between treatments was achieved in a re-analysis undertaken with agreement by the FDA that included all available post-treatment SCr data (Section 2.4.1).
- REVERSE (97 subjects treated with terlipressin; 99 subjects treated with placebo) did not achieve its prespecified endpoint of Confirmed HRS Reversal (Table 1), but the results did favor terlipressin for this endpoint. In addition, there was a clinically meaningful improvement in overall renal function (prespecified endpoint of change in SCr from baseline to EOT) compared with placebo.

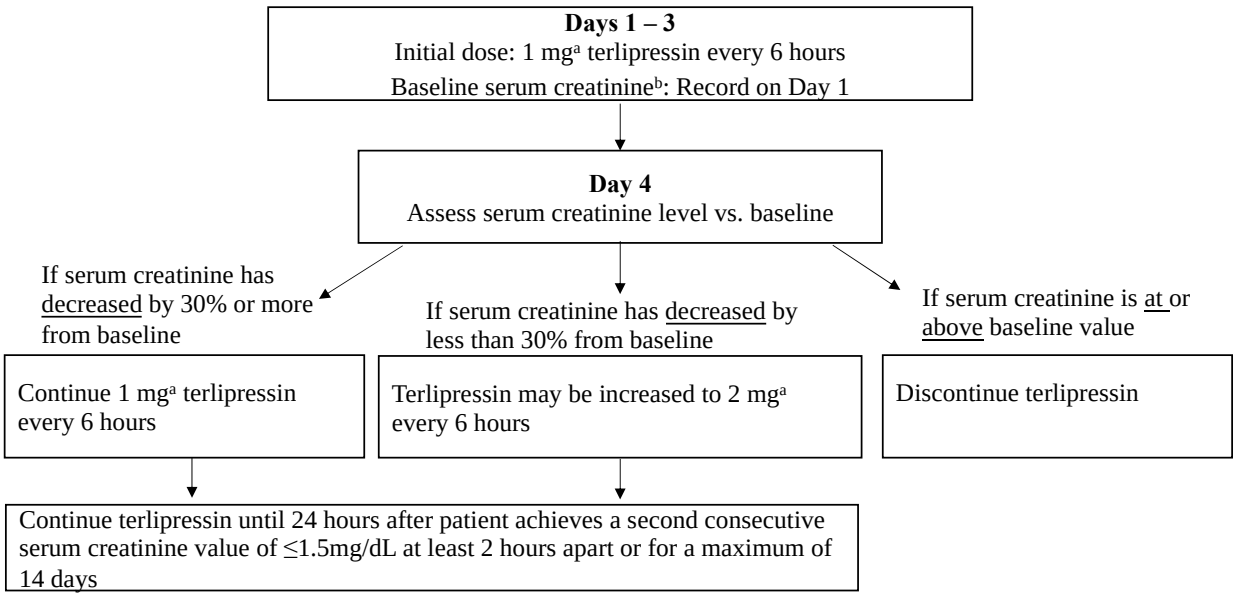
All 3 studies enrolled subjects in the US; CONFIRM and REVERSE also enrolled subjects in Canada, and OT-0401 also enrolled subjects in Russia and Germany. Of the total number of subjects randomized into the phase 3 studies (N=608), 561 (92.3%) were enrolled in the US, 31 (5.1%) were enrolled in Canada, 9 (1.5%) were enrolled in Russia, and 7 (1.2%) were enrolled in Germany. The US, Canada, and Germany are countries with similar clinical practice for the management of patients with HRS-1. Supportive medical treatment at the Russian sites in OT-0401 differed from other sites (eg, no antibiotic administration or treatment of encephalopathy and lack of access to liver transplant); however, the proportion of Russian subjects is less than 2% of the overall population, so these differences did not impact the overall results.

The clinical development program for terlipressin also included appropriate Nonclinical and Clinical Pharmacology programs, summarized in Sections 3 and 4, respectively.

2.6 Dosing Regimen

The proposed dosing regimen for terlipressin (Figure 7) for the treatment of adults with HRS-1 is based on the clinical development program and extensive worldwide clinical history of treating these patients with this product.

Figure 7. Proposed Dosing Regimen for Terlipressin in HRS-1



SCr, serum creatinine.
a. Expressed as the acetate salt. 0.85-mg terlipressin is equivalent to 1-mg terlipressin acetate.
b. Baseline SCr is the last available SCr before administration of the first dose.

The recommended starting dose is 1 mg terlipressin acetate given q6h by bolus injection over a period of approximately 2 minutes. On Day 4, SCr should be assessed for response compared to baseline. If SCr has not decreased by at least 30% from the baseline value, the dose of terlipressin may be doubled to 2 mg q6h. If SCr is at or above baseline, treatment should be discontinued.

Terlipressin should be used with caution in patients with dyspnea, tachypnea, or respiratory distress, and patients should be closely monitored for pulmonary edema. The dose should not be increased in patients with severe pre-existing cardiovascular disease or in the presence of an ongoing significant AE, such as ischemia.

Serum creatinine levels should be monitored daily to assess response to therapy. Treatment with terlipressin should continue until 24 hours after 2 consecutive SCr ≤1.5 mg/dL values or a maximum of 14 days. Re-treatment for up to an additional 14 days can be initiated if HRS-1 recurs after previous successful treatment with terlipressin.

Management of AEs may require temporary interruption, dose reduction, or permanent discontinuation of terlipressin. Following temporary interruption, when symptoms resolve,

terlipressin may be re-instituted at a lower dose or at a less frequent dosing interval. The lowest doses used in the clinical studies ranged from 2 to 3 mg/day.

Intravascular volume depletion should be addressed before starting therapy with any vasopressor. In the clinical studies, it was recommended that terlipressin should be administered with albumin based on ICA guidelines (Salerno 2007).

3 NONCLINICAL SUMMARY

HRS-1 is a rare serious condition with no available therapy. The duration of terlipressin administration is short (IV bolus q6h typically for 6 days up to a maximum of 14 days), and there are substantial clinical and nonclinical data on terlipressin and related compounds available in the literature. Therefore, it was agreed with FDA that terlipressin could be evaluated in an abbreviated nonclinical program complemented by supportive evidence from the literature.

3.1 Toxicology Studies

The toxicology program conducted by the original sponsor comprised 2 4-week good laboratory practices (GLP) toxicology studies in rats and dogs, including toxicokinetics; 3 GLP genotoxicity studies; and 1 GLP human red blood cell fragility study.

The nonclinical pharmacokinetic (PK) studies demonstrated that the PK profile of terlipressin following IV administration is similar in animals and in humans. The in vivo metabolic conversion of terlipressin to lysine-vasopressin and the similar PK profile of terlipressin following IV administration in animals and in humans demonstrate that rats and dogs are appropriate animal models to study the pharmacology and toxicology of terlipressin. Depending on the doses and species studied, the observed exposure to terlipressin and lysine-vasopressin in the toxicology studies compared with that seen in humans and ranged from 1- to 17-fold higher in dogs and 3- to 100-fold higher in rats.

Single-dose toxicity studies were conducted in mice, rats, and dogs. In mice, a single dose of 500 mg/kg IV was estimated to be the maximum tolerated dose (MTD) for terlipressin. In rats, a single-dose of 2 mg/kg IV was considered to be the MTD for terlipressin. In dogs, the MTD for terlipressin was considered to be 0.3 mg/kg/day IV.

Repeat-dose toxicity studies were conducted in rats and dogs. In a 7-day dose range-finding study in rats, the MTD for terlipressin was considered to be 2 mg/kg/day for 7 days. In a 7-day dose range-finding study in dogs, the MTD for terlipressin was considered to be 0.3 mg/kg/day.

Pivotal 28-day repeat dose toxicity studies were conducted in rats and dogs. Terlipressin doses of 0, 0.15, 0.5, and 1.5 mg/kg/day, administered once daily, were selected for use in the 28-day rat study. Terlipressin doses of 0, 0.0625, 0.125, and 0.25 mg/kg/day were selected for use in the 28-day dog study; terlipressin was administered twice daily (BID).

Overall, the toxicology study findings were consistent with the known pharmacologic effects of terlipressin and its metabolite lysine-vasopressin (a potent vasoconstrictor hormone) mediated through V_1 receptor activity at the high doses studied. These effects are dose dependent, generally reversible, and of a short duration that coincides with the peak plasma concentrations. Overall, the cutaneous, GI, and respiratory effects seen in the toxicology studies in rats and dogs were consistent with the side effect profile observed in the clinical studies.

In dogs, terlipressin doses up to 0.125 mg/kg/day did not have a toxicologic effect on ECG recordings. At the highest administered dose, the maximum serum concentration (C_{max}) of terlipressin in the studied dogs was 5-fold greater than the C_{max} for the proposed starting dose (1 mg q6h) in humans. The C_{max} for lysine-vasopressin at the maximum dose was 7-fold greater in dogs than that in humans at the proposed starting dose. There was no significant difference in corrected QT interval (QTc) in any dose group compared with control (n=8 per group). Although there was no overall difference in QTc in the high-dose group (0.25 mg/kg; n=8), in male dogs (n=4) there was a statistically significant increase in QTc (average 41 msec) observed when compared with the male control group (n=4). The increase in QTc intervals in male dogs was not dose related, and the small sample size makes it difficult to draw firm conclusions. In the clinical study OT-0401, analysis of ECG data concluded that terlipressin may have a small effect on QTc, using Fridericia's formula (QTcF), of approximately 8 msec relative to placebo (see Section 4.2.1). In contrast to the findings in dogs, in the clinical study OT-0401, female HRS-1 subjects had small increases in QTcF, whereas male HRS-1 subjects had small decreases in QTcF. The small increase in QTcF interval with terlipressin compared with placebo observed in OT-0401 was not associated with an increase in relevant cardiac AEs.

Terlipressin has no mutagenic or clastogenic activity.

Pharmacodynamic (PD) studies in rats and pregnant guinea pigs have shown that terlipressin reduces blood flow to the uterus. The adverse effects of vasopressins, including terlipressin, in human and animal pregnancies are based on their mechanism of action, which may result in uterine contractions and endometrial ischemia; these risks are appropriately captured in the proposed labeling.

In conclusion, the toxicology data are consistent with the clinical study findings in humans and support the use of terlipressin for the treatment of HRS-1 patients.

4 CLINICAL PHARMACOLOGY

4.1 Terlipressin Pharmacology

Terlipressin is a synthetic vasopressin analog derived from the natural hormone lysine-vasopressin. It differs from endogenous human vasopressin by the substitution of lysine for arginine at the eighth position of the endogenous molecule and the addition of 3 glycyl residues at the amino terminus.

The duration of action of terlipressin is longer than that of vasopressin, due to sequential cleavage of the N-terminal glycyl residues by various tissue peptidases, resulting in gradual release of the pharmacologically active metabolite lysine-vasopressin. Terlipressin acts on vasopressin V_1 receptors both as a prodrug for lysine-vasopressin and with pharmacologic activity of its own, albeit with lower potency (1%) relative to lysine-vasopressin (Pliska 1976, Blei 1980, Forsling 1980, Nilsson 1990, Plate 1995, Wisniewski 2006, Koshimizu 2012). Once formed, lysine-vasopressin is rapidly eliminated via various peptidase-mediated routes, primarily in the liver and kidney, associated with a loss of pressor activity (Lauson 1967, Fabian 1969, Forsling 1980, Carone 1987, Nilsson 1990, Plate 1995, Fjellestad-Paulsen 1996, Jackson 2005). Because of the ubiquitous nature of peptidases in body tissues, it is unlikely that the metabolism of terlipressin is affected by disease state or other drugs.

Specific pharmacology studies of terlipressin have not been conducted by the sponsor, as agreed with the FDA in the original pre-IND meeting in January 2004. Because terlipressin is a vasopressin analog, the pharmacology of terlipressin can be derived from the well-known profile of vasopressin based on a large body of published data (Thibonnier 2002, Holmes 2003, Holmes 2004, Kam 2004, Jackson 2005).

Arginine-vasopressin is the main endogenous hormone that regulates body fluid osmolality in humans and most mammals; lysine-vasopressin is the endogenous antidiuretic hormone in pigs. Vasopressin has multiple actions in various tissues. It is a direct systemic vasoconstrictor (mediated by V_1 receptor-activation on vascular smooth muscle cells), and an antidiuretic (mediated by V_2 receptor-activation in the renal collecting duct system). Antidiuretic V_2 receptor-mediated effects of vasopressin occur at concentrations far lower than those required to induce V_1 vascular receptor-mediated effects. In addition, low plasma concentrations of vasopressin induce vasodilation in coronary, cerebral, and pulmonary arterial circulations mediated by endothelial oxytocin receptors, which release nitric oxide.

The half-life and potency of lysine-vasopressin is similar to that of arginine-vasopressin (Fabian 1969, Wisniewski 2006), except that the antidiuretic activity of lysine-vasopressin may have a somewhat shorter duration than that of arginine-vasopressin (Fabian 1969). In competitive binding assays, arginine-vasopressin bound to V_1 and V_2 receptors with similar high affinities. Lysine-vasopressin also bound to these vasopressin receptors with high affinity; however, it

bound to the V_1 receptor with approximately 6-fold higher affinity than to the V_2 receptor. Terlipressin bound to the vasopressin receptors with low affinity, and, like lysine-vasopressin, terlipressin bound to the V_1 receptor with approximately 6-fold higher affinity than to the V_2 receptor.

4.2 Pharmacodynamics

Findings from the terlipressin clinical program demonstrate the relevant PD properties of terlipressin. In patients with HRS-1, terlipressin increases MAP and normalizes endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system), resulting in increased renal blood flow. Consequent to the increase in MAP, there is also an associated decrease in heart rate.

After IV administration of the first dose of 1 mg of terlipressin in REVERSE and CONFIRM, increases in predose diastolic and systolic blood pressure and MAP and a decrease in heart rate were evident in most subjects by 5 minutes. These changes were maintained for at least 6 hours after administration. The maximum change in these vital signs occurred 1.2–2 hours after the first dose.

After administration of the last dose of 1 mg of terlipressin in CONFIRM, an increase from predose diastolic, systolic, and MAP and a decrease from predose heart rate were evident in most subjects by 5 minutes. The maximum change in vital signs occurred 0.7-1 hour after the last dose.

Maximum plasma terlipressin and lysine-vasopressin concentrations were reached at approximately 5 minutes (ie, at the end of the IV bolus injection) and approximately 1 hour, respectively. The time of maximum change in blood pressure and heart rate occurred at approximately the same time as maximum lysine-vasopressin plasma concentrations. Changes in blood pressure and heart rate that occurred 5 minutes after treatment with terlipressin were likely attributable to the effect of terlipressin; maintaining these effects for 6 hours after treatment was most likely attributable to the formation of lysine-vasopressin.

The effect of terlipressin on vasoactive hormones was evaluated in OT-0401 and in the literature. These studies have shown that in subjects with cirrhosis and HRS-1, treatment with terlipressin tends to normalize the activity of endogenous vasoconstrictor systems.

4.2.1 QTc Substudy

The effect of terlipressin on QTc intervals was evaluated in 41 HRS-1 subjects in OT-0401. It was agreed with the FDA at the pre-IND meeting (January 2004) that the potential for QT prolongation could be evaluated through the collection of paired electrocardiograms (ECGs) at baseline, on the study days on which peak drug concentrations were expected (Days 3 and 7), and at EOT or Day 14.

The mean differences in change from baseline between terlipressin- and placebo-treated subjects at Day 3 were a 2.9 msec and 7.8 msec increase using Bazett's and Fridericia's corrections, respectively. Both increases resulted not from an absolute increase in the QTc interval for subjects in the terlipressin group but rather from a greater decrease in QTc interval in placebo subjects compared to terlipressin subjects.

A linear mixed-effects model was used to investigate the potential relationship between QTc intervals and terlipressin plasma concentrations. For this PK/PD analysis, there were 153 ECG measurements from 28 patients. The effect of terlipressin plasma concentrations on QTc intervals was not statistically significant. When QTc changes from baseline of each patient were evaluated, the effect of terlipressin plasma concentrations was also not significant.

In general, patients with cirrhosis have a high prevalence of prolonged QT intervals. Against this potentially confounding background, the small increases seen with terlipressin compared with placebo in a limited group of subjects is unlikely to be of clinical relevance in the setting of HRS-1 (Bernardi 1998, Puthumana 2001, Trevisani 2003, Yap 2003, FDA Guidance for Industry 2005, Zambruni 2006).

4.3 Pharmacokinetics

The PK profile of terlipressin is well characterized in the literature and through the clinical development program. The linear PK of terlipressin in healthy subjects has been demonstrated in the literature (Forsling 1980, Nilsson 1990) and align with the findings from the clinical program in HRS-1 subjects.

Pharmacokinetic data were assessed from 2 well-controlled safety and efficacy studies, REVERSE and OT-0401. Conventional PK studies that employ extensive blood sampling procedures were not feasible or practical because of the hyperdynamic state of the subjects with HRS-1; therefore, sparse PK sampling was implemented in both REVERSE and OT-0401. Population PK modeling was conducted on the sparse samples from a total of 227 terlipressin plasma samples and 246 lysine-vasopressin plasma samples from 69 HRS-1 patients to characterize the PK of terlipressin and lysine-vasopressin and to identify the source of variability in PK of terlipressin and lysine-vasopressin in HRS-1 patients.

The half-life of terlipressin was estimated to be 0.9 hours and that of its active metabolite, lysine-vasopressin, 3.0 hours. The longer apparent half-life of lysine-vasopressin compared to injection of lysine-vasopressin itself most likely reflects the metabolic conversion from terlipressin to lysine-vasopressin (a flip-flop kinetic).

In the population PK study, age, sex, CrCl, Child-Pugh-Turcotte score, serum alkaline phosphatase, serum alanine or aspartate aminotransferase, or total bilirubin did not significantly affect clearance of either terlipressin or lysine-vasopressin. No covariate effect was found on the volume of distribution for either terlipressin or lysine-vasopressin.

The extent of renal or hepatic impairment did not significantly affect clearance of either terlipressin or its active metabolite. This may be because terlipressin conversion to lysine-vasopressin depends upon tissue peptidases and entails further breakdown into amino acids, with minimal renal elimination of either terlipressin or lysine-vasopressin.

CrCl was used as an indicator of renal function for each subject in the population PK analysis. The median CrCl was 30 mL/min and ranged from 9.7-57.6 mL/min. The majority of subjects had moderate or severe renal impairment due to the nature of the disease. CrCl had no effect on any of the PK parameters of terlipressin or lysine-vasopressin.

Severity of hepatic function had an insignificant effect on any of the PK parameters of terlipressin and lysine-vasopressin. Since the conversion of terlipressin to lysine-vasopressin is not dependent on the liver, hepatic function is not expected to be an important factor affecting the clearance of terlipressin or lysine-vasopressin.

Body weight was the only significant covariate identified in the population PK analysis. However, body weight had no effect on the clearance of lysine-vasopressin. Population PK simulation of 1000 replicates of 69 subjects was performed to inspect the body weight (range of 43-170 kg) effect on the exposures of terlipressin and lysine-vasopressin at steady state (average concentration within 1 dosing interval). The simulation outcome suggested that although terlipressin exposure decreases with increasing body weight, the change in active metabolite (lysine-vasopressin) level with body weight is negligible. Lysine-vasopressin is pharmacologically more potent than terlipressin and, therefore, no body-weight based dosage adjustment of terlipressin is required.

4.3.1 Drug-Drug Interactions and Antigenicity

4.3.1.1 Pharmacokinetic Drug-Drug Interactions

Terlipressin and lysine-vasopressin, are predominately metabolized via various peptidases in body tissues and not in blood or plasma (Plate 1995). Accordingly, a series of in vitro studies indicated that cytochrome P450 inducers or inhibitors will not alter the PK of terlipressin or lysine-vasopressin. Terlipressin and lysine-vasopressin are not anticipated to alter the PK of cytochrome P450 substrates or to affect human ATP-binding cassette (ABC) and solute carrier (SLC) transporters (membrane-bound proteins whose functions include moving substrates into and out of cells). No formal clinical drug interaction study was conducted.

4.3.1.2 Pharmacodynamic Drug-Drug Interactions

Potential PD interactions of terlipressin with other selected vasoactive drugs (octreotide, prazosin, nitroglycerin, and atrial natriuretic peptide [ANP]) have been reported in the literature. Octreotide did not modify the systemic hemodynamic effects of terlipressin, and the combination of octreotide and terlipressin did not exert an additive effect in reducing the hepatic venous pressure gradient (HVPG, Lin 2002). The combination of prazosin and terlipressin resulted in a

more profound reduction of the HVPG than did terlipressin alone. Prazosin did not modify the systemic hemodynamic effects of terlipressin (Lee 2001). Nitroglycerin reversed the systemic hemodynamic effects of terlipressin without any further reduction in the HVPG. Nitrates had been added to terlipressin empirically in an attempt to avoid the vasoconstrictive adverse reactions that were observed with vasopressin; however, it is recommended that nitrates not be routinely added to terlipressin in the treatment of acute variceal bleeding (Ioannou 2003). In subjects with cirrhosis, refractory ascites is associated with a blunted natriuretic response to exogenous ANP, which appears to be related to ANP-induced arterial hypotension. Therefore, the effect of terlipressin was investigated in combination with ANP. Combined therapy did not change MAP or renal perfusion pressure but did increase urine output and sodium excretion compared with terlipressin alone (Gadano 1997).

4.3.1.3 Antigenicity

The potential antigenicity of terlipressin was evaluated in OT-0401. No significant level of antibody to terlipressin was detected in any samples tested.

4.4 Clinical Pharmacology Data Relevant to Dose Recommendation

The dosing regimen utilized in the 3 randomized, controlled studies has demonstrated efficacy with a manageable safety profile. This is a starting dose of 1 mg q6h, titrated upwards to 2 mg q6h in case of a <30% decrease in SCr from baseline. Terlipressin dosing may be interrupted and/or decreased to manage toxicity. The dosing regimen was originally based on HRS-1 clinical studies published in the literature. These literature data were further supported by a small, academic-sponsored study in HRS-1 subjects included in the original NDA (TAHRS 2008), where it was observed that no patient responded at a dose of 0.5 mg every 4 hours (q4h) and all required an increase to 1 mg q4h. In the 3 NDA studies, the majority of patients responded at a dose of 1 mg, and some patients required a 2-mg dose for response. The 2-mg dose, with a slightly higher incidence of specific SAEs compared with the 1-mg dose, was determined to have an overall reasonable safety profile.

Of the 117 terlipressin-treated subjects who achieved HRS Reversal in the pooled phase 3 population, 67.5% achieved response at the 1-mg q6h starting dose. A total of 32.5% of subjects required escalation to the 2-mg q6h dose in order to achieve HRS Reversal. In further analysis of the data by dose received, the incidence of HRS Reversal was 31.2% of subjects who stayed at the 1-mg dose and 40% of those who escalated to 2 mg.

From a safety perspective, there was no overall dose-related increase in AEs or SAEs for subjects initially receiving the 1-mg dose who escalated to the 2 mg dose. However, specific SAEs were increased in subjects escalated to the 2-mg dose: MODS, abdominal pain, hepatic encephalopathy, acute kidney injury, and fluid overload. This increase in SAE incidence was minimal: 2-4% greater with the higher dose.

These data support the recommendation of the starting dose which is titrated for efficacy and safety.

4.5 Clinical Pharmacology Conclusions

The PK, PD, and PK/PD relationship of terlipressin are established in the literature and well characterized in the clinical development program.

Terlipressin is a potent, synthetic vasopressin analogue with 6-times greater selectivity for vasopressin V_1 receptors than V_2 receptors. It is a prodrug that produces its active metabolite, lysine-vasopressin, gradually upon dosing.

Terlipressin modifies systemic hemodynamics primarily by increasing MAP. The sustained increase in MAP from baseline to end of treatment was associated with reversal of HRS-1.

Terlipressin plasma concentration does not have a statistically significant effect on QTc intervals, and terlipressin does not have a clinically relevant effect on QTc in HRS-1 subjects.

Terlipressin exhibits PK linearity in healthy subjects, and the PK of HRS-1 subjects in the clinical studies was consistent with those of earlier studies in healthy volunteers.

A population PK study showed no statistically significant or clinically relevant effect of renal or hepatic function on terlipressin or lysine-vasopressin clearance in HRS-1 subjects.

Body weight affects terlipressin clearance but not lysine-vasopressin clearance. Because lysine-vasopressin is pharmacologically more active than terlipressin, adjustment of dosing for body weight is not required.

Terlipressin and lysine-vasopressin have no PK potential for drug-drug interactions regarding cytochrome P450 pathways or SLC or ABC transporters. The PD drug-drug interactions with other vasoactive drugs are known and predictable.

The safe and effective starting dose and titration regimen for terlipressin in HRS-1 patients has been established and supported by the evidence of the 3 clinical studies.

5 EFFICACY

5.1 Clinical Studies of Terlipressin in HRS-1

5.1.1 Clinical Development

The clinical development program for terlipressin for the treatment of subjects with HRS-1 comprises 1 pivotal phase 3 study (CONFIRM), 1 supportive phase 3 efficacy study (OT-0401), that provides confirmatory evidence of efficacy based on the re-analysis using the full dataset of its primary endpoint, and a phase 3 study (REVERSE) that provides additional efficacy data. All 3 studies were randomized, double-blind, placebo-controlled, multicenter studies that had a similar primary endpoint focused on successful treatment of HRS-1.

These 3 studies provide evidence of the efficacy of terlipressin in HRS-1 (Table 5). The positive results from the pivotal CONFIRM study and the supportive OT-0401 study based on the re-analysis form the regulatory basis for approval of terlipressin. The REVERSE study provides additional supportive efficacy and safety data. Although the REVERSE study did not meet the primary endpoint of Confirmed HRS Reversal, it demonstrated a clinically meaningful improvement in overall renal function when compared with placebo. The other predefined endpoint of lower SCr levels from baseline to EOT was achieved.

The primary endpoint of successful treatment of HRS-1 evolved during the clinical development program from OT-0401 to REVERSE to CONFIRM.

Table 5. Clinical Studies of Terlipressin in HRS-1

Study/Dates	Subjects, n	Primary Efficacy Endpoint	Primary Efficacy Results
CONFIRM July 13, 2016-July 24, 2019	N=300; n=199 terlipressin, n=101 placebo	Verified HRS Reversal comprising 3 components: 1. Two consecutive SCr values ≤1.5 mg/dL collected ≥2 h apart, while receiving study treatment (inclusive of up to 24 h after last dose of study drug) by Day 14 or hospital discharge, prior to any RRT, TIPS, liver transplant, or open-label vasopressor *and* 2. Subject alive ≥10 d after achieving the 2 consecutive SCr values ≤1.5 mg/dL collected ≥2 h apart *and* 3. Subject did not require any RRT for ≥10 days after achieving the 2 consecutive SCr values of ≤1.5 mg/dL collected ≥2h apart. 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	Verified HRS Reversal: terlipressin 29.1%, placebo 15.8%; Z score=2.52618, corresponding to p=0.012

Table 5. Clinical Studies of Terlipressin in HRS-1

Study/Dates	Subjects, n	Primary Efficacy Endpoint	Primary Efficacy Results
		enrolled on or after 17 August 2018. SCr values were included if obtained after the administration of a single dose of dobutamine.	
OT-0401 Sept 22,2004-August 28, 2006	N=112; n=56 terlipressin, n=56 placebo	Treatment Success at Day 14 comprising 2 components: 1. Subject alive with a reversal of HRS (SCr ≤1.5 mg/dL on ≥2 measurements collected 48 (±8) h apart) *and* 2. Without dialysis or recurrence of HRS	Treatment Success at Day 14 (ITT): terlipressin 25%, placebo 12.5%; p=0.093 Re-analysis including all Day 14 SCr values (ITT): terlipressin 28.6%, placebo 12.5%; p=0.037
REVERSE Oct 11, 2010-May 10, 2013	N=196; n=97 terlipressin, n=99 placebo	Confirmed HRS Reversal comprising 2 components: 1. Two SCr values ≤1.5 mg/dL collected ≥2 d apart, while receiving study treatment *and* 2. Without intervening RRT or liver transplant	Confirmed HRS Reversal: terlipressin 19.6%, placebo 13.1%; p=0.2214

HRS-1, hepatorenal syndrome type 1; ITT, intent-to-treat; q6h, every 6 hours; RRT, renal replacement therapy; SCr, serum creatinine.

5.1.2 Key Study Design Features of the CONFIRM, OT-0401, and REVERSE Studies

The designs of the 3 phase 3 studies were similar (Table 6). Subjects were randomized 2:1 to terlipressin or placebo in CONFIRM and 1:1 to terlipressin or placebo in OT-0401 and REVERSE. Each of the studies had a primary endpoint focused on successful treatment of HRS-1 and included other assessments of renal function and survival.

Table 6. Key Study Design Features of Phase 3 Studies of Terlipressin Conducted in Subjects with HRS-1

	CONFIRM	OT-0401	REVERSE
Design	Phase 3, randomized, double-blind, placebo-controlled, multicenter		
Randomization[a]	2:1	1:1	1:1
Subjects, n/sites, n	300/60	112/35	196/52
Stratification	Qualifying SCr (<3.4 or ≥3.4 mg/dL) and pre-enrollment LVP (≥1 event of ≥4 or <4 L within 3-14 d prior to randomization	Presence or absence of alcoholic hepatitis	Qualifying SCr (<3.6 or ≥3.6 mg/dL) and presence or absence of alcoholic hepatitis
Treatment	Placebo or terlipressin acetate 1 mg IV q6h with increase to 2 mg q6h if SCr decreased to meet specific criteria, total of 4-8 mg/d. All subjects received albumin therapy.		

Table 6. Key Study Design Features of Phase 3 Studies of Terlipressin Conducted in Subjects with HRS-1

	CONFIRM	OT-0401	REVERSE
Duration of treatment	• Treatment continued until 24 h after 2 consecutive SCr values of ≤1.5 mg/dL were obtained ≥2 h apart or up to a maximum of 14 d (15 d if SCr first reached 1.5 mg/dL on Day 14)	• Treatment continued until ≥2 SCr values ≤1.5 mg/dL were obtained at least 48 h apart, or up to 14 d	• Treatment continued until 24 h after 2 consecutive SCr values of ≤1.5 mg/dL were obtained ≥2 h apart or ≤14 d • New provision of 15 or 16 d for those subjects who respond on Day 13 or 14, respectively
Dose modification and discontinuation	• If on Day 4 of therapy (≥10 doses), SCr had decreased, but by <30% from the BL value, the dose was increased to 2 mg q6h • If on Day 4 (≥10 doses), SCr was ≥BL value, study medication was discontinued	• If after 3 days of therapy (≥12 doses), SCr had not decreased by ≥30% from the BL value, the dose was increased to 2 mg q6h • Dosing was terminated if subject was a treatment failure (reached criteria for RRT at any time during treatment or SCr was ≥BL at ≥Day 7)	• If on Day 4 of therapy (≥10 doses), SCr had decreased, but by <30% from the BL value, the dose was increased to 2 mg q6h • If on Day 4 (≥10 doses), SCr was ≥BL value, study medication was discontinued
Key efficacy endpoints	• Renal function: Verified HRS Reversal[b]; HRS Reversal; change in SCr from BL • Durability of HRS Reversal • Incidence of RRT	• Renal function: Treatment Success at Day 14[b]; HRS Reversal; change in SCr from BL; Confirmed HRS Reversal (post-hoc analysis)	• Renal function: Confirmed HRS Reversal[b]; HRS Reversal; change in SCr from BL

BL, baseline; CrCl, creatinine clearance; GI, gastrointestinal; HRS, hepatorenal syndrome; LVP, large volume paracentesis; q6h, every 6 hours; RRT, renal replacement therapy; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome.
a. Terlipressin:placebo ratio.
b. Primary endpoint.

Definitions of the endpoints are provided in the individual study discussions.

5.1.3 Study Population

The study population of these studies consisted of adult subjects with cirrhosis, ascites, and a diagnosis of HRS-1 based on treatment guidelines available at the time (Arroyo 1996, Salerno 2007, Angeli 2015a; Table 7). All subjects had a rapidly progressive reduction in renal function with no sustained improvement in renal function during the pre-enrollment screening phase. In OT-0401, sustained pre-enrollment improvement in renal function was defined as a decrease of SCr to ≤1.5 mg/dL or an increase in CrCl to ≥40 mL/min after diuretic withdrawal and plasma

volume expansion with 1.5 L isotonic saline or albumin. These criteria were refined in CONFIRM and REVERSE. In these studies, all subjects underwent fluid challenge with IV albumin to demonstrate that volume expansion was insufficient to correct renal failure. Additionally, specific inclusion criteria were applied for the SCr response 48 hours after diuretic withdrawal and albumin administration (<20% decrease in SCr and SCr ≥2.25 mg/dL) in order to avoid enrollment of subjects responding to albumin alone. These subjects were acutely and critically ill with severe underlying disease, multiple comorbidities, and had undergone multiple therapeutic interventions.

Table 7. Study Population in the Phase 3 Studies of Terlipressin Conducted in Subjects with HRS-1

	CONFIRM	OT-0401	REVERSE
Key Inclusion Criteria			
Diagnosis of HRS-1	Based on the 2007 and 2015 ICA guidelines and discussions with FDA during the SPA procedure. The ICA criteria for diagnosis of HRS-1 are based on exclusion of other causes of renal failure in subjects with cirrhosis and ascites (for complete ICA diagnostic criteria, see Salerno 2007 and Angeli 2015a)	Based on 1996 ICA diagnostic criteria for HRS-1 (Arroyo 1996), together with some additional clarifications discussed with FDA, used as the basis for the protocol inclusion and exclusion criteria	Based on updated 2007 ICA diagnostic criteria for HRS-1 (Salerno 2007), together with experience gained from the OT-0401 study and discussions with FDA at an End of Review Conference (13 January 2010) and during the SPA procedure (19 April 2010), used as the basis for the protocol inclusion and exclusion criteria
Rapidly progressive reduction in renal function	SCr of ≥2.25 mg/dL and met a trajectory for SCr to double over 2 wk. Doubling of SCr within 2 wk (or for shorter durations, SCr values over time met slope-based criteria for proportional increases likely to be representative of at least a doubling within 2 wk)	Doubling of SCr to ≥2.5 mg/dL within 2 wk or a 50% reduction of the initial 24-h CrCl to a level <20 mL/min in the absence of all other causes of renal impairment	SCr ≥2.5 mg/dL and/or a doubling of SCr within 2 wk (or for shorter durations, SCr values over time meeting slope-based criteria for proportional increases likely to be representative of at least a doubling within 2 wk; SCr values had to be documented ≥4 days)
SCr at randomization	≥2.25 mg/dL	≥2.5 mg/dL	≥2.5 mg/dL
No sustained improvement in renal function	<20% decrease in SCr and SCr of ≥2.25 mg/dL ≥48 h after both diuretic withdrawal and the beginning of plasma volume expansion with albumin	No decrease of SCr to ≤1.5 mg/dL or no increase in CrCl to ≥40 mL/min after diuretic withdrawal and plasma volume expansion with 1.5 L isotonic saline	<20% decrease in SCr and SCr ≥2.25 mg/dL ≥48 h after both diuretic withdrawal and the beginning of plasma volume expansion with albumin
Prior midodrine/ octreotide	No washout required	No washout required	48-h washout required

Table 7. Study Population in the Phase 3 Studies of Terlipressin Conducted in Subjects with HRS-1

	CONFIRM	OT-0401	REVERSE
Key Exclusion Criteria			
SCr	>7.0 mg/dL	No upper limit	≥7.0 mg/dL
LVP	≥1 event of LVP of ≥4 L within 2 d of randomization	No LVP criteria for exclusion	No LVP criteria for exclusion
Shock	Ongoing shock	Ongoing shock	Ongoing shock
Uncontrolled infection or sepsis	Sepsis and/or uncontrolled bacterial infection	Uncontrolled (ongoing) bacterial infection	Sepsis and/or uncontrolled bacterial infection
Anti-infective therapy	<2 days of anti-infective therapy for documented or suspected infection.	White blood cell counts had not decreased by 2-3 days after antibiotic treatment	Requirement for ≥2 days of anti-infective therapy for suspected or documented infection
Fluid losses	None specified	Current fluid losses (ie, GI fluid losses due to repeat vomiting or intense diarrhea) or renal fluid losses (eg, weight loss >500 g/d for several days in subjects with ascites without peripheral edema or 1000 g/d in those with peripheral edema)	No exclusion based on current fluid losses

CrCl, creatinine clearance; FDA, Food and Drug Administration; GI, gastrointestinal; HRS-1, hepatorenal syndrome type 1; ICA, International Club of Ascites; LVP, large volume paracentesis; SCr, serum creatinine; SPA, Special Protocol Assessment; wk, week.

5.1.4 Treatment

All 3 studies used the same starting dose of terlipressin (1 mg q6h) and allowed an increase in dose to 2 mg q6 if SCr had decreased by <30% from baseline after a predefined time period. Dosing was titrated upwards to try to achieve a response and discontinued if there was no decrease in SCr after a predefined time period.

In all 3 studies, study medication was continued for 24 hours (CONFIRM) to 2 days (REVERSE and OT-0401) after a first value of SCr ≤1.5 mg/dL had been obtained or up to a maximum of 14 days, with the exception that a maximum of 15 or 16 days was allowed in CONFIRM and REVERSE if SCr first reached 1.5 mg/dL on Day 13 or 14, respectively.

In OT-0401, study drug was discontinued if the SCr value was greater than or equal to baseline on treatment Day 7. In CONFIRM and REVERSE, study treatment was discontinued if on Day 4 (after >10 doses) SCr was greater than or equal to the subject's baseline value. This stopping rule

was based on the observation in OT-0401 that the majority of subjects who would ultimately respond had some SCr decrease by Day 3 of therapy.

In all 3 studies, study drug was permanently discontinued if either RRT or transplantation was scheduled. Based upon experience from OT-0401, the REVERSE protocol required permanent discontinuation of study drug if any ischemic AE occurred, and CONFIRM required permanent discontinuation if mesenteric or cardiac ischemic events occurred. In both of the later studies, the dose could not be increased in the setting of circulatory overload, pulmonary edema, treatment-refractory bronchospasm, or known coronary artery disease (CAD). If dosing was interrupted because of a non-ischemic AE, terlipressin could be restarted at the investigator's discretion at the same or lower dose of 0.5-1 mg q6h. The studies allowed retreatment 1 time at the investigator's discretion with the initially assigned study medication if HRS-1 recurred following at least a partial initial response, defined as ≥30% decrease in SCr from baseline in CONFIRM and REVERSE. In the OT-0401 protocol, a partial response was defined as >50% decrease in SCr from baseline value during treatment but SCr >1.5 mg/dL in patients alive at Day 14.

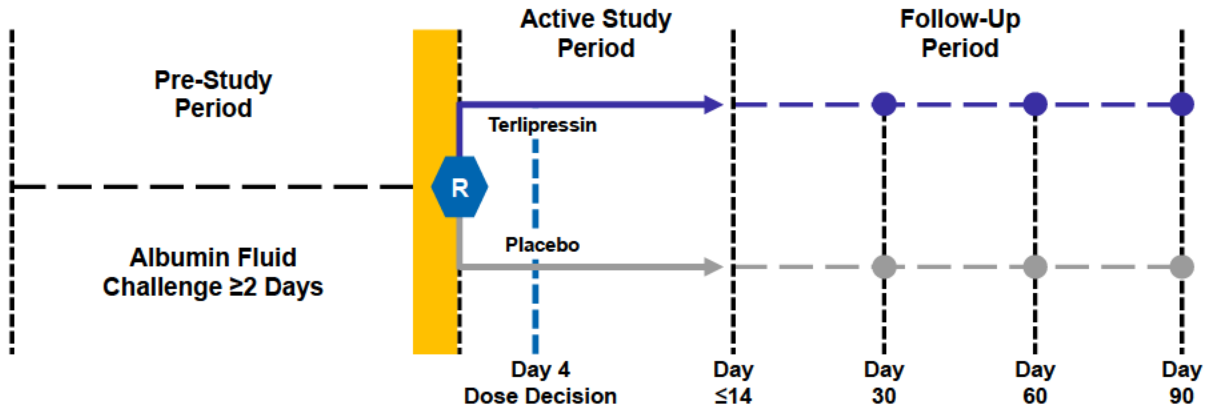
The CONFIRM and REVERSE study protocols complied with the ICA recommendations for the diagnosis of HRS (Salerno, 2007) and the OT-0401 study was in accordance with standard medical practice at the time (Arroyo 1996). Albumin was strongly recommended as per disease state guidelines and subjects in both treatment groups received standard-of-care albumin therapy.

5.2 CONFIRM Study

5.2.1 CONFIRM Study Design

The pivotal CONFIRM study was the largest prospective, placebo-controlled study in HRS-1 to date and included 300 subjects treated for up to 14 days with a follow-up period of 90 days (Figure 8). The first subject was enrolled on July 13, 2016 and the last subject completed the study on July 24, 2019.

Figure 8. CONFIRM Study Design



BL, baseline; SCr, serum creatinine.
Dosing decision: Initial treatment of study drug of 1 mg q6h was increased to 2 mg on Day 4 if SCr <BL but decrease was not >30%. The dose was not increased in subjects with coronary artery disease or in the setting of circulatory overload, pulmonary edema, or bronchospasm. Study drug was stopped if SCr ≥BL. Additionally, all subjects received standard of care albumin.

This study was conducted under a SPA agreement with a primary endpoint of Verified HRS Reversal (See Table 5).Verified HRS Reversal ensures that the first SCr value of no more than 1.5 mg/dL was not a spurious laboratory value and the HRS Reversal was durable and clinically meaningful.

5.2.2 Study Population

The primary population for analysis of efficacy endpoints was the intent-to-treat (ITT) population, defined as all randomized subjects.

5.2.3 Subject Disposition and Discontinuation From Treatment

Overall, 300 subjects were enrolled and randomized 2:1 to treatment with terlipressin (n=199) or placebo (n=101). A total of 139 (46.3%) subjects (87 [43.7%] terlipressin; 52 [51.5%] placebo) in the ITT population completed the study through Day 90. The most frequent reasons for treatment discontinuation were Verified HRS Reversal in the terlipressin group and SCr ≥ baseline value in the placebo group (Table 8).

Table 8. Reasons for Discontinuation of Study Treatment in the CONFIRM Study (ITT Population)

	Terlipressin (N=199) n (%)	Placebo (N=101) n (%)	Total (N=300) n (%)
Received maximum duration of randomized study medication treatment per protocol	11 (5.5)	6 (5.9)	17 (5.7)
Verified HRS Reversal	72 (36.2)	17 (16.8)	89 (29.7)
Transplant	9 (4.5)	3 (3.0)	12 (4.0)
Renal replacement therapy	13 (6.5)	9 (8.9)	22 (7.3)
Death	4 (2.0)	0 (0.0)	4 (1.3)
SCr at or above baseline value	42 (21.1)	36 (35.6)	78 (26.0)
Request of subject or legally authorized representative	7 (3.5)	5 (5.0)	12 (4.0)
Hospice / comfort / palliative care	7 (3.5)	2 (2.0)	9 (3.0)
Adverse event	19 (9.5)	4 (4.0)	23 (7.7)
Transjugular intrahepatic portosystemic shunt	1 (0.5)	0 (0.0)	1 (0.3)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent for study participation, including follow-up	4 (2.0)	1 (1.0)	5 (1.7)
Physician decision	10 (5.0)	14 (13.9)	24 (8.0)
Other	7 (3.5)	6 (5.9)	13 (4.3)
Discharge	6 (3.0)	1 (1.0)	7 (2.3)
Randomized not dosed	0 (0.0)	1 (1.0)	1 (0.3)
No improvement in SCr / other therapies initiated / withdrew from treatment	1 (0.5)	4 (4.0)	5 (1.7)

HRS, hepatorenal syndrome; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group; SCr, serum creatinine.

5.2.4 Baseline Characteristics and Demographics

In the ITT population, the demographics and baseline characteristics were comparable between the terlipressin- and placebo-treatment groups (Table 9).

Table 9. Baseline Characteristics and Demographics in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101
Age, y		
Mean (SD)	54.0 (11.34)	53.6 (11.83)
Median	54.7	54.5
Minimum, maximum	23.2, 78.0	30.6, 81.6

Table 9. Baseline Characteristics and Demographics in the CONFIRM Study (ITT Population)

	Terlipressin N=199	**Placebo N=101**
Sex, n (%)		
Male	120 (60.3)	59 (58.4)
Female	79 (39.7)	42 (41.6)
Ethnicity, n (%)		
Hispanic or Latino	32 (16.1)	13 (12.9)
Not Hispanic or Latino	165 (82.9)	88 (87.1)
Race, n (%)		
American Indian or Alaskan native	2 (1.0)	0
Asian	5 (2.5)	1 (1.0)
Black or African American	12 (6.0)	5 (5.0)
Native Hawaiian or other Pacific islander	0	0
White	177 (88.9)	94 (93.1)
Alcoholic hepatitis, n (%)		
Present	81 (40.7)	39 (38.6)
Not present	118 (59.3)	62 (61.4)
Qualifying SCr, n (%)		
<3.4 mg/dL	111 (55.8)	55 (54.5)
≥3.4 mg/dL	88 (44.2)	46 (45.5)
Baseline SCr, mg/dL		
Mean (SD)	3.5 (1.01)	3.5 (1.06)
Median	3.3	3.3
Minimum, maximum	2.3, 6.9	2.1, 6.2
LVP strata, n (%)		
<4 L	123 (61.8)	59 (58.4)
≥4 L	76 (38.2)	42 (41.6)
Mean (SD) Baseline CLIF-SOFA score	10.4 (2.4)	10.8 (2.5)
Baseline ACLF grade, n (%)		
0	0	0
1	99 (49.7)	41 (40.6)
2	60 (30.2)	42 (41.6)
3	40 (20.1)	18 (17.8)
Baseline bilirubin, mg/dL		
N	188	99
Mean (SD)	13.0 (13.4)	15.2 (15.8)
Median	6.0	8.4
Minimum, maximum	0.3, 51.6	0.7, 98.0
SIRS, n (%)	84 (42.2)	48 (47.5)
Baseline MAP (SD), mm Hg	78.7 (12.08)	77.5 (9.36)
Baseline MAP <65 mm Hg, n (%)	24 (12.1)	9 (8.9)

Table 9. Baseline Characteristics and Demographics in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101
Baseline MELD score		
N	177	88
Mean (SD)	32.7 (6.6)	33.1 (6.2)
Median	34.0	34.0
Minimum, maximum	16.0, 40.0	17.0, 40.0
Baseline Child-Pugh-Turcotte score		
N	194	95
Mean (SD)	10.0 (1.9)	10.2 (1.9)
Class A [5-6]	3 (1.5)	2 (2.0)
Class B [7-9]	68 (34.2)	32 (31.7)
Class C [10-15]	123 (61.8)	61 (60.4)
Missing	5 (2.5)	6 (5.9)

ACLF, acute-on-chronic liver failure; CLIF-SOFA, chronic liver failure-sepsis organ failure assessment; ITT, intent-to-treat; LVP, large volume paracentesis; MAP, mean arterial pressure; MELD, model for end-stage liver disease; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

The etiology of cirrhosis was similar in the 2 treatment groups (Table 10). Alcohol was the most frequent cause of cirrhosis in both treatment groups, followed by non-alcoholic steatohepatitis. More patients with hepatitis C were randomized into the terlipressin group.

Table 10. Hepatic History in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101
Etiology of cirrhosis (n,%)		
Alcohol	134 (67.3)	67 (66.3)
Hepatitis B	4 (2.0)	1 (1.0)
Hepatitis C	31 (15.6)	7 (6.9)
Non-alcoholic steatohepatitis	42 (21.1)	24 (23.8)
Autoimmune hepatitis	10 (5.0)	5 (5.0)
Primary biliary cirrhosis	5 (2.5)	3 (3.0)
Cryptogenic	6 (3.0)	3 (3.0)
Other	9 (4.5)	5 (5.0)
Ascites grade, n (%)		
1	51 (25.6)	19 (18.8)
2	81 (40.7)	35 (34.7)
3	66 (33.2)	46 (45.5)

Table 10. Hepatic History in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101
Alcoholic hepatitis, n (%)	81 (40.7)	39 (38.6)
Hepatocellular carcinoma, n (%)	13 (6.5)	5 (5.0)
Milan criteria, n (%)		
No	4 (2.0)	3 (3.0)
Single lesion ≤2 cm	1 (0.5)	1 (1.0)
Single lesion >2 cm and ≤5 cm	6 (3.0)	1 (1.0)
≤3 lesions; none >3 cm	2 (1.0)	0 (0.0)
Esophageal varices, n (%)		
Prior history of esophageal variceal hemorrhage	30 (15.1)	21 (20.8)
Received esophageal banding treatment	48 (24.1)	29 (28.7)
Received TIPS	7 (3.5)	2 (2.0)

ITT, intent-to-treat; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; TIPS, transjugular intrahepatic portosystemic shunt.

5.2.5 Statistical Analysis

5.2.5.1 Primary Endpoint of Verified HRS Reversal

Verified HRS Reversal by treatment group was analyzed using a Z score based on the upper alpha boundary values for the interim and final analyses. If the Z score was >2.79651 for the interim analysis of the first 150 patients, the study would stop for early success. The study continued because the interim analysis was not successful. For success, the Z score of the final analysis had to be >1.97743. No imputation was performed for missing data in CONFIRM and there was no missing data for the primary endpoint in CONFIRM.

5.2.5.2 Multiple Testing for the Final Analysis of the Secondary Endpoint Analyses

A Hochberg procedure (Hochberg 1988) for multiple testing and the alpha level corresponding to the Z score of the primary efficacy analysis were used for testing the secondary efficacy analyses at the final analysis. After ordering the p-values of the 4 secondary endpoints from largest to smallest, the values were tested with the largest p-value compared with an alpha of 0.047993, the second largest p-value compared with 0.023997, the third largest p-value compared with 0.015998, and the smallest p-value, compared with 0.011998. If the largest p-value was less than alpha, all 4 secondary endpoint analyses were significant; if not, the second p-value was to be tested against the alpha comparator. If the second largest p-value was less than alpha, the remaining 3 secondary endpoint analyses were significant. Testing continued through the list until a p-value was found that was less than its comparator alpha or the testing of all 4 was complete.

5.2.5.3 Change from Baseline to EOT in Renal Function

Change from baseline through EOT in SCr was analyzed using repeated measures analysis of covariance (ANCOVA) based on a mixed-effect model (Verbeke 2000; Mallinckrodt 2003). This mixed-effects model repeated method analysis used maximum likelihood (ML) estimation, compound symmetry covariance matrix, and repeated statement with a factor of subject nested in strata. Factors used in the model included treatment, qualifying SCr (<3.4 or ≥3.4 mg/dL), LVP ≥4 L within 14 days of randomization (at least 1 event of ≥4 L or <4 L within 14 days prior to randomization), day, and the treatment-by-day interaction. SCr values are excluded after RRT, TIPS, liver transplant, or open-label vasopressor use. Only SCr collected after treatment start date through 24 hours after treatment end date are included. No imputation methods were used for missing SCr values.

The treatment-by-day interaction was tested separately at the 0.10 level of significance from the same model. If treatment-by-day interaction was significant, estimates and p-values for treatment differences within each day were produced, but the primary test of the treatment effect was the overall treatment effect p-value. If the treatment-by-day interaction was significant, this analysis was also to be performed without the interaction as a sensitivity analysis.

5.2.6 Efficacy Results in the ITT Population

5.2.6.1 Verified HRS Reversal

5.2.6.1.1 Primary Endpoint

The first component of Verified HRS Reversal, 2 consecutive SCr values of ≤1.5 mg/dL, demonstrates a robust and clinically significant improvement in renal function. The second component, absence of RRT for ≥10 days, emphasizes the durability of this improvement in renal function. The third component, survival for ≥10 days after second confirmatory SCr value, establishes the effect of treatment on a key clinical outcome of initial survival. Combined, the 3 components provide a strong, clinically meaningful measure of efficacy in the setting of multiple competing comorbidities. This endpoint was designed in close collaboration with FDA to ensure that the HRS Reversal was durable and clinically meaningful.

Verified HRS Reversal was achieved in significantly more subjects in the terlipressin group (29.1%) than in the placebo group (15.8%); the difference between groups was statistically significant with a Z score of 2.52518, corresponding to a p-value of 0.012 (Table 11). This near doubling of HRS Reversal is clinically meaningful.

Table 11. Verified HRS Reversal in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101	Z score[a]
Verified HRS Reversal, n (%)	58 (29.1)	16 (15.8)	2.52618
95% CI	0.2, 0.4	0.1, 0.2	

CI, confidence interval; HRS, hepatorenal syndrome; ITT, intent-to-treat; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; RRT, renal replacement therapy; SCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic shunt.
a. The final analysis was successful if the Z score >1.97743. A Z score of 2.52618 corresponds to p=0.012.
Note: Any SCr values obtained after liver transplantation, RRT, TIPS, or open-label vasopressor use are excluded. Serum creatinine values obtained after a single dose administration of dobutamine or after midodrine administration are 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 17 August 2018.

5.2.6.2 Secondary Endpoints

The results of all 4 prespecified secondary endpoint analyses favored terlipressin. Three were statistically significant in favor of terlipressin: HRS Reversal; durability of HRS Reversal, defined as incidence of HRS Reversal without RRT to Day 30; and HRS Reversal in subjects with SIRS (Table 12). Verified HRS Reversal without HRS recurrence by Day 30 was achieved by a higher percentage of subjects in the terlipressin group than the placebo group, although the difference was not statistically significant.

In the terlipressin group, 10 of 58 subjects (17.2%) with Verified HRS Reversal experienced a recurrence of HRS by Day 30. Of these 10 subjects, 5 were retreated with terlipressin, and 3 of the 5 responded again with HRS Reversal.

Table 12. Secondary Endpoint Results in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101	p-value[a]
HRS Reversal, n (%)	72 (36.2)	17 (16.8)	<0.001
95% CI	0.3, 0.4	0.1, 0.2	
Durability of HRS Reversal, n (%)	63 (31.7)	16 (15.8)	0.003
95% CI	0.3, 0.4	0.1, 0.2	
SIRS subgroup	N=84	N=48	
HRS Reversal, n (%)	28 (33.3)	3 (6.3)	<0.001
95% CI	0.2, 0.4	0.0, 0.1	
Verified HRS Reversal without HRS recurrence by Day 30, n (%)	N=199	N=101	
	48 (24.1)	16 (15.8)	0.092
95% CI	0.2, 0.3	0.1, 0.2	

CI, confidence interval; HRS, hepatorenal syndrome; ITT, intent-to-treat; LVP, large volume paracentesis; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; RRT, renal replacement therapy; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome; TIPS, transjugular intrahepatic portosystemic shunt.

a. Cochran-Mantel-Haenszel test stratified by qualifying SCr (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (≥1 event of ≥4 vs <4 L).

Note: The incidence of HRS Reversal: percentage of subjects with a SCr value ≤1.5 mg/dL while on treatment (on treatment defined as up to 24 hours after the final dose of study drug) by Day 14 or discharge. Durability of HRS Reversal: percentage of subjects with HRS Reversal (as defined above) without RRT to Day 30. Verified HRS Reversal without HRS recurrence by Day 30: percentage of subjects with verified HRS Reversal who did not experience a recurrence of HRS by Day 30. SCr values after RRT, TIPS placement, liver transplant, or open-label vasopressor treatment were excluded from these analyses.

5.2.6.3 Additional Prespecified Renal Function Endpoints

Restoration of renal function is the most important goal of treatment in HRS-1 patients. Improvement of renal function was assessed with 5 prespecified endpoints: response to treatment based on the International Club of Ascites-acute kidney injury (ICA-AKI) 2015 response definitions, change from baseline to EOT in SCr, incidence of a >30% improvement in SCr from baseline at EOT, SCr data collected after hospital discharge, and change from baseline to EOT in CrCl (Table 13). Nominal p-values are presented for informational purposes.

The 2015 ICA-AKI “complete and partial response” definitions do not have the fixed 1.5 mg/dL SCr cut-off used in the criteria for HRS Reversal, but rather assess improvement in renal function with respect to each subject’s baseline SCr value. These response definitions have important implications in patient management, because cirrhotic patients with diabetes and hypertension who develop HRS-1 may have chronic kidney disease with baseline SCr values >1.5 mg/dL. A complete response was defined as a reduction of SCr to ≤0.3 mg/dL above the

baseline value, and a partial response was a reduction of SCr to ≥0.3 mg/dL above the baseline value. A significantly higher percentage of subjects had a complete response in the terlipressin group compared with the placebo group (nominal p<0.001; Table 13).

The repeated measures analysis results of the change in SCr level from baseline through EOT with adjustment for interaction between treatment and day for the ITT population was used to assess the impact of stratified treatment cohort (qualifying SCr), duration of therapy, alcoholic hepatitis, and treatment-by-day on improvement in SCr. If the results were significant with this adjustment for interaction, a sensitivity analysis was conducted without adjusting for interaction. Although the SCr decreased in both treatment groups from baseline to EOT, the reduction was significantly larger in the terlipressin group than in the placebo group (nominal p<0.001) for the treatment difference both with and without adjustment for the interaction (Table 13, Figure 9). The baseline SCr level is defined as the last SCr prior to the start of study drug. In Figure 9, most baseline values are from Day 1, resulting in fewer changes from baseline values for Day 1.

A significantly higher percentage of subjects in the terlipressin group compared with the placebo group had a >30% improvement in SCr (nominal p<0.001; Table 13). In CONFIRM, ≥30% SCr improvement was a prespecified endpoint and another measure of clinically meaningful improvement in renal function. This endpoint was designed based on literature evidence that worsening of SCr, by even small increments, leads to increased short term morbidity and mortality in patients with AKI (Coca 2007, Mehta 2007, Nadim 2012) and allows assessment of significant improvement in renal function, irrespective of HRS Reversal. While all efforts were made to ensure in CONFIRM that enrolled subjects have a historic SCr ≤1.5 so that if there is a response to treatment, they have a realistic chance to achieve verified HRS Reversal. In certain cases, for example subjects with AKI stage 3 (SCr 4) at time of randomization, significant improvement in SCr may occur but the subject may not get to 1.5 threshold if their new baseline SCr is 1.7 mg/dL. Across the 3 clinical studies, significantly more subjects achieved ≥30% improvement in SCr on terlipressin than those on placebo. Also, the outcomes for those subjects who achieved this threshold of improvement was significantly better than those who didn't.

A nominally significantly larger increase in CrCl was also observed in the terlipressin group compared with the placebo group (Table 13, Figure 10). All of these endpoints demonstrated that terlipressin improved renal function, which is clinically important in this severely compromised population.

Table 13. Additional Prespecified Endpoint Results in the CONFIRM Study (ITT Population)

	Terlipressin N=199 n (%)	**Placebo N=101 n (%)**	**Nominal p-value**
ICA-AKI Complete response (return of SCr to a value ≤0.3 mg/dL above the baseline value)[a]	61 (30.7)	10 (9.9)	<0.001[b]
ICA-AKI partial response	32 (16.1)	13 (12.9)	
ICA-AKI no response	106 (53.3)	78 (77.2)	
Change in SCr from BL to EOT	N=192	N=98	
Without interaction between treatment and day			
LS mean (SE)[c]	-0.9 (0.06)	-0.4 (0.08)	<0.001[d]
95% CI	-1.06, -0.83	-0.55, -0.26	
With interaction between treatment and day			
LS mean (SE)[e]	-1.0 (0.06)	-0.3 (0.08)	<0.001[d]
95% CI	-1.12, -0.86	-0.44, -0.12	
>30% improvement in SCr	87 (43.7%)	22 (21.8%)	<0.001
SCr levels post-discharge[f]			
N	111	58	
Mean (SD)	2.4 (1.48)	2.3 (2.08)	
Median (minimum, maximum)	1.9 (0.5, 7.2)	1.5 (0.6, 13.2)	
Change in CrCl from BL to EOT	N=187	N=93	
Without interaction between treatment and day			
LS mean (SE)[c]	19.7 (1.11)	12.5 (1.48)	<0.001[d]
95% CI	17.51, 21.88	9.60, 15.42	

Table 13. Additional Prespecified Endpoint Results in the CONFIRM Study (ITT Population)

	Terlipressin N=199 n (%)	Placebo N=101 n (%)	Nominal p-value
With interaction between treatment and day			
LS mean (SE)[e]	20.5 (1.25)	9.7 (1.57)	<0.001[d]
95% CI	18.02, 22.95	6.61, 12.78	

BL, baseline; CI, confidence interval; CrCl, creatinine clearance; EOT, end of treatment; IAC-AKI, International Club of Ascites-acute kidney injury; ITT, intent-to-treat; LS, least squares; LVP, large volume paracentesis; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; SCr, serum creatinine; SD, standard deviation; SE, standard error.

a. IAC-AKI response definition: complete (full) response defined as the return of SCr to a value ≤0.3 mg/dL above the baseline value; partial response is a reduction of SCr to ≥0.3 mg/dL above the baseline value.

b. From a Cochran-Mantel-Haenszel Test stratified by qualifying SCr (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (≥1event of ≥4 vs <4 L).

c. From repeated measures analysis of covariance as implemented in Proc Mixed with factors of treatment, qualifying SCr (<3.4 vs ≥3.4 mg/dL), prior LVP within 14 days of randomization (≥1 event of ≥4 vs <4 L), and day.

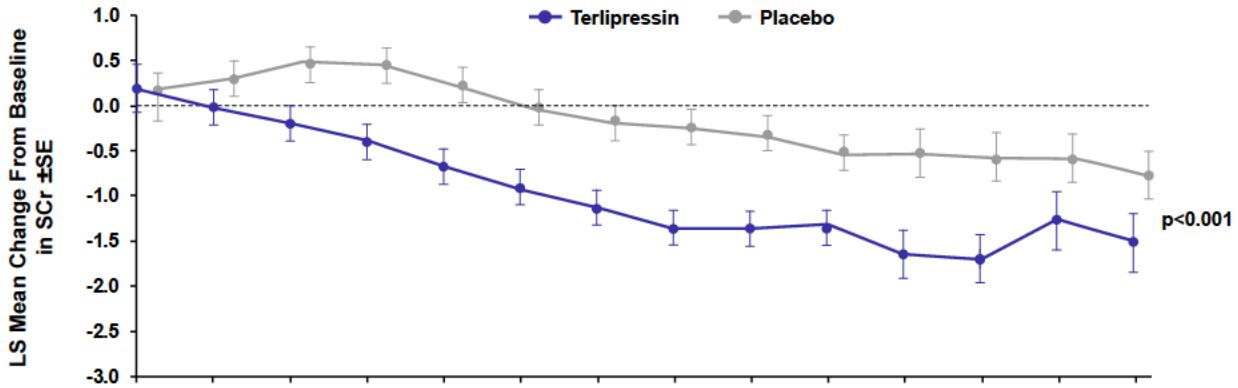
d. For terlipressin LS mean change from BL minus placebo LS mean change from BL.

e. From repeated measures analysis of covariance as implemented in Proc Mixed with factors of treatment, qualifying SCr (<3.4 vs ≥3.4 mg/dL), prior LVP within 14 days of randomization (≥1 event of ≥4 vs <4 L), day, and the treatment-by-day interaction.

f. For subjects retreated prior to the Day 30 follow-up visit, the SCr value is the highest SCr value from the pretreatment period of the retreatment cycle and the Day 30 follow-up visit of the original treatment cycle.

Note: SCr values after renal replacement therapy, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressors use are excluded. Only CrCl collected after treatment start date through 24 hours after treatment end date are included. Repeated measures analysis of covariance model uses compound symmetry covariance matrix, maximum likelihood estimation, and repeated statement with a factor of subject nested in strata.

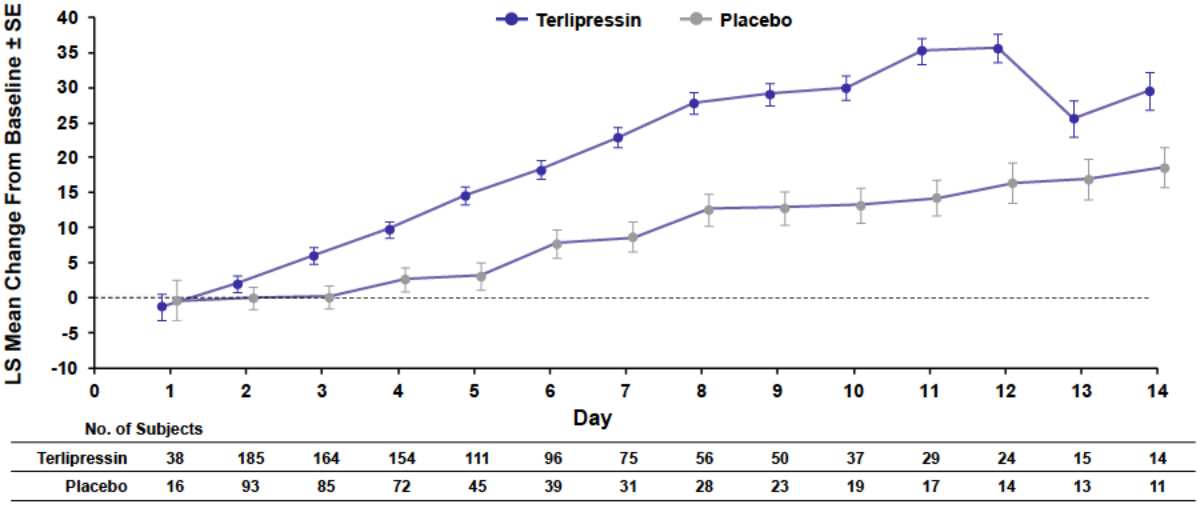
Figure 9. Repeated Measures Analysis of Change from Baseline in SCr Level by Day in the CONFIRM Study (ITT Population)



Patients, n														
Terlipressin	39	190	168	157	114	98	76	56	50	37	29	24	15	14
Placebo	18	98	89	74	45	39	31	28	23	19	17	14	13	11

ITT, intent-to-treat; LS, least squares; SCr, serum creatinine; SE, standard error.
P-value is nominal. No imputation methods were used for missing SCr values.
SCr values after renal replacement therapy, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressors use are excluded. Only SCr collected after treatment start date through 24 hours after treatment end date are included. SCr was measured at least once per day. Baseline SCr was defined as the last SCr prior to the start of study drug. As a result, there were fewer patients with changes from baseline values for Day 1.

Figure 10. Repeated Measures Analysis of Change from Baseline in CrCl Level by Day in the CONFIRM Study (ITT Population)



No. of Subjects														
Terlipressin	38	185	164	154	111	96	75	56	50	37	29	24	15	14
Placebo	16	93	85	72	45	39	31	28	23	19	17	14	13	11

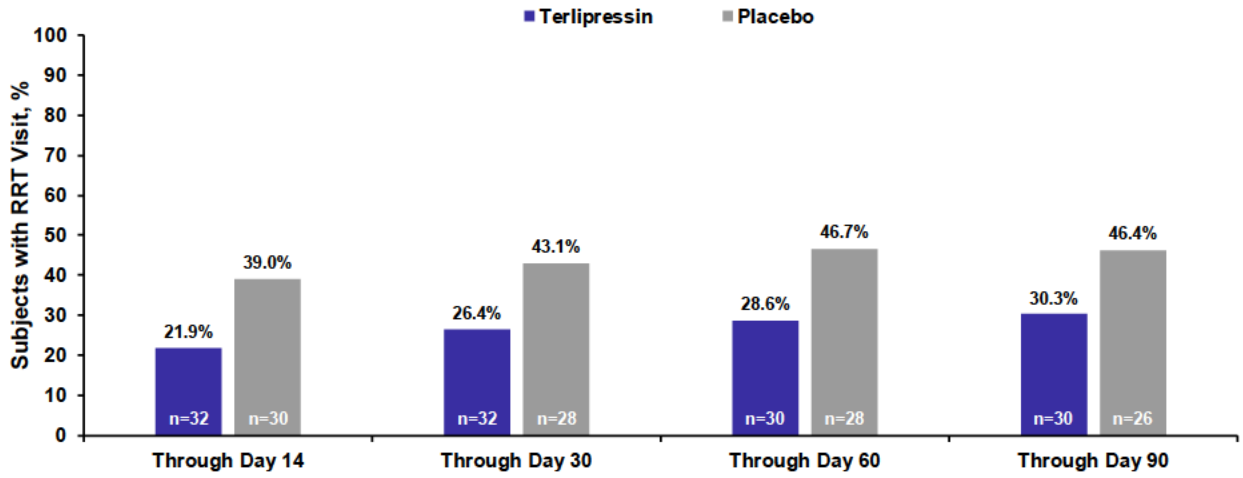
CrCl, creatinine clearance; ITT, intent-to-treat; LS, least squares; LVP, large volume paracentesis; RRT, renal replacement therapy; SCr, serum creatinine; SE, standard error.
CrCl values after RRT, transjugular intrahepatic portosystemic shunt, liver transplant, or open-label vasopressors use are excluded.
LS means from repeated measures analysis of covariance as implemented in Proc Mixed with factors of treatment, qualifying SCr, LVP ≥4 L within 14 days at randomization, day, and the treatment-by-day interaction. Model uses compound symmetry covariance matrix, maximum likelihood estimation, and repeated statement with factor of subject nested in the strata.

5.2.6.4 Clinical Endpoints

5.2.6.4.1 Need for Renal Replacement Therapy

Incidence of RRT in subjects alive at each time point shows fewer subjects requiring RRT in the terlipressin group compared with the placebo group, with a difference between groups at all time points in this post-hoc analysis (Figure 11).

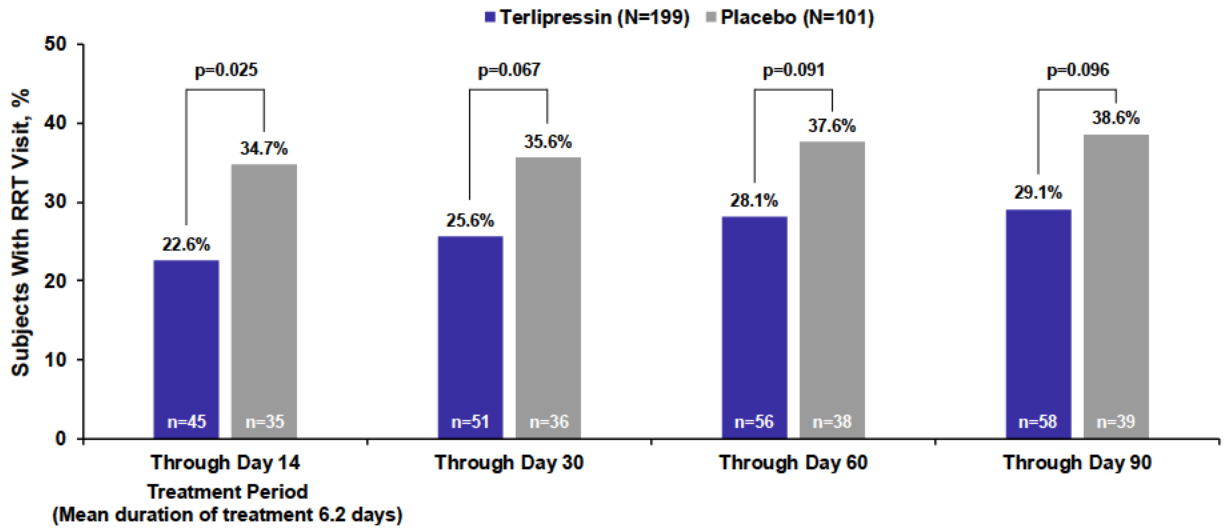
Figure 11. Incidence of RRT in Subjects Alive Through Day 90 in the CONFIRM Study (ITT Population)



ITT, intent-to-treat; RRT, renal replacement therapy.

Incidence of RRT through Day 90 was a prespecified end point in CONFIRM. At each time point assessed, including follow-up time points, the proportion of subjects needing RRT was lower in the terlipressin group than the placebo group, with a statistically significant difference between the groups during treatment through Day 14 (Figure 12). All p-values are nominal in the analysis presented.

Figure 12. Cumulative Incidence of RRT Through Day 90 in the CONFIRM Study (ITT Population)



ITT, intent-to-treat; LVP, large volume paracentesis; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; RRT, renal replacement therapy.
p-values from a Cochran-Mantel-Haenszel test stratified by qualifying SCr (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (≥1 event of ≥4 vs <4 L).

5.2.6.4.2 Incidence of RRT in Subjects With Fluid Overload

In CONFIRM, the incidence of RRT was also assessed in a subset of subjects with reported fluid overload. RRT is an invasive intervention that may be required in patients who fail recommended first-line management with fluid restriction and diuretics.

While fluid overload was the most common indication for RRT in both subject subsets during the first 14 days of the study, the incidence of RRT was still lower in terlipressin-treated subjects than in placebo-treated subjects with fluid overload (Table 14). The clinical benefit of reduction in need for RRT was maintained, even in this subgroup of patients in CONFIRM.

Table 14. Incidence of RRT for Fluid Overload in CONFIRM (ITT Population)

	Terlipressin N=69 n (%)	Placebo N=19 n (%)
Incidence of RRT in subjects with fluid overload		
RRT by Day 14	16 (23.2)	9 (47.4)
RRT by Day 30	17 (24.6)	9 (47.4)
RRT by Day 60	17 (24.6)	10 (52.6)
RRT by Day 90	17 (24.6)	10 (52.6)
Indication of RRT up to Day 14		
Any reason for RRT	16 (23.2)	8 (42.1)
Fluid overload	10 (14.5)	3 (15.8)
Pulmonary edema	4 (5.8)	2 (10.5)
Hyperkalemia	0	1 (5.3)
Metabolic acidosis	2 (2.9)	1 (5.3)
Uremia	2 (2.9)	1 (5.3)
Other	3 (4.3)	2 (10.5)

RRT, renal replacement therapy.

5.2.6.5 Additional Clinical Outcomes

As requested by FDA, additional post-hoc analyses were conducted to identify favorable trends in clinical outcomes thought to be predicted by the SCr-based surrogate endpoint of verified HRS Reversal, including length of hospitalization and ICU stay.

5.2.6.5.1 Hospitalization and ICU Outcomes

5.2.6.5.1.1 Hospitalization Length of Stay

The majority of HRS-1 patients are expected to have a lengthy hospital stay even if HRS-1 is reversed by an intervention. The mean total length of hospital stay was similar in the 2 treatment groups (Table 15).

Table 15. Hospitalization Length of Stay in the CONFIRM Study (ITT Population)

	Terlipressin N=199	**Placebo N=101**
Length of study site hospital stay, days		
N	199	101
Mean (SD)	24.5 (19.00)	24.8 (18.27)
Median	19.0	21.0
Minimum, maximum	4.0, 172.0	4.0, 117.0
Time from randomization to study site hospital discharge, days		
N	143	73
Mean (SD)	17.8 (18.64)	19.3 (17.21)
Median	13.0	15.0
Minimum, maximum	3.0, 169.0	2.0, 91.0

ITT, intent-to-treat; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; SD, standard deviation.

5.2.6.5.1.2 ICU Length of Stay

While similar percentages of subjects in each treatment group were admitted to the ICU, subjects in the terlipressin group had approximately half the time in the ICU as the placebo group (Table 16). Similarly, the mean time from randomization to discharge from the ICU was about half as long in the terlipressin group as in the placebo group.

Table 16. ICU Length of Stay in the CONFIRM Study (ITT Population)

	Terlipressin N=199	Placebo N=101
Incidence of ICU admission, n (%)	31 (15.6)	14 (13.9)
Length of ICU stay, days		
N	31	14
Mean (SD)	6.4 (5.53)	13.2 (15.92)
Median	4.0	8.0
Minimum, maximum	1.0, 28.0	2.0, 59.0
Time from randomization to ICU discharge, days		
N	18	9
Mean (SD)	9.9 (6.24)	18.7 (17.99)
Median	9.0	12.0
Minimum, maximum	3.0, 29.0	2.0, 60.0

ICU, intensive care unit; ITT, intent-to-treat; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group; SD, standard deviation.

In subjects admitted to the ICU, a greater proportion of terlipressin-treated subjects than placebo-treated subjects were alive at Days 14 and 30 without RRT or transplant (Table 17).

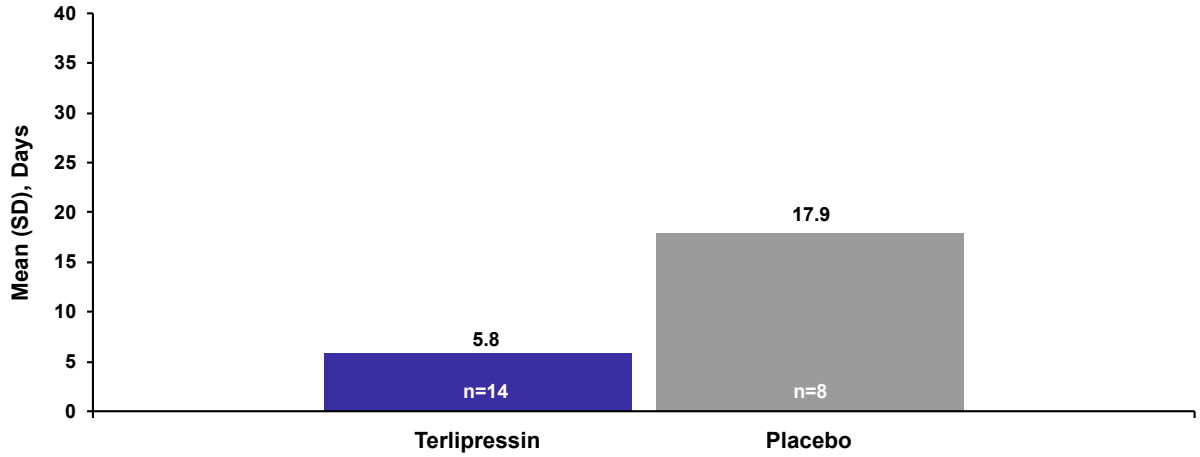
Table 17. Outcomes for Subjects Admitted to the ICU in the CONFIRM Study (ITT Population)

	Terlipressin N=31	Placebo N=14
Alive without RRT or transplant at Day 14	9 (29.0)	1 (7.1)
Alive without RRT or transplant at Day 30	4 (12.9)	0 (0.0)

ICU, intensive care unit; ITT, intent-to-treat; RRT, renal replacement therapy.

In subjects alive at Day 90, the length of ICU stay was also shorter with terlipressin treatment than placebo treatment (Figure 13).

Figure 13. ICU Length of Stay in Subjects Alive at Day 90 in the CONFIRM Study (ITT Population)



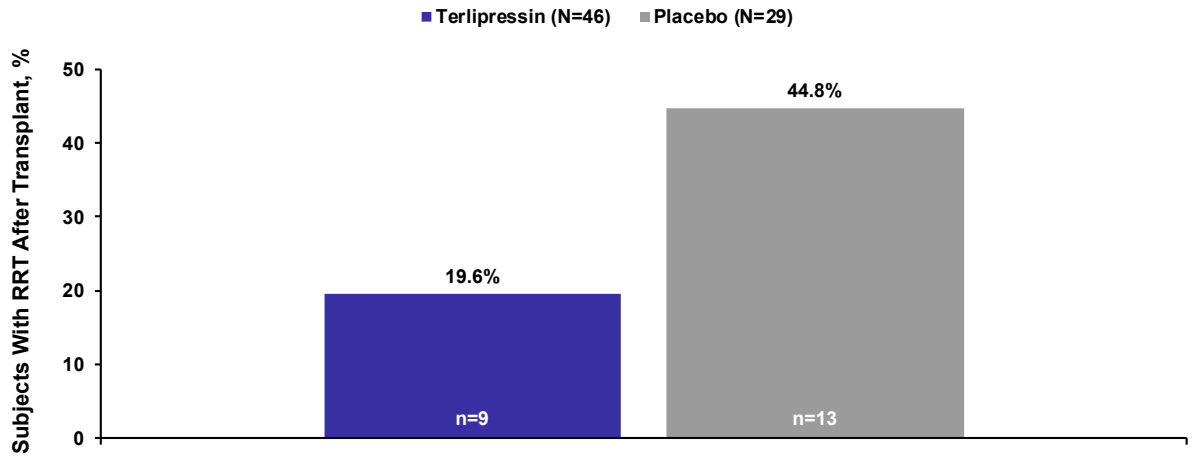
ICU, intensive care unit; ITT, intent-to-treat; SD, standard deviation.

5.2.7 Liver Transplant Outcomes

Liver transplant is the only definitive treatment for advanced decompensated cirrhosis, the underlying clinical milieu within which HRS-1 develops (EASL 2018, Runyon 2013). However, only a minority of HRS-1 patients are eligible for or able to have liver transplantation, and organs are not always available in time. Based on UNOS data, there were roughly 8,200 liver transplants performed in 2019 (OPTN 2020), and there are approximately 35,000 patients in the US annually with HRS-1 (Pant 2016). Hence, most subjects aren't liver transplant candidate or receive a transplant in a timely manner.

Post liver transplant, a substantially lower incidence of RRT was observed in the terlipressin group compared with the placebo group (Figure 14).

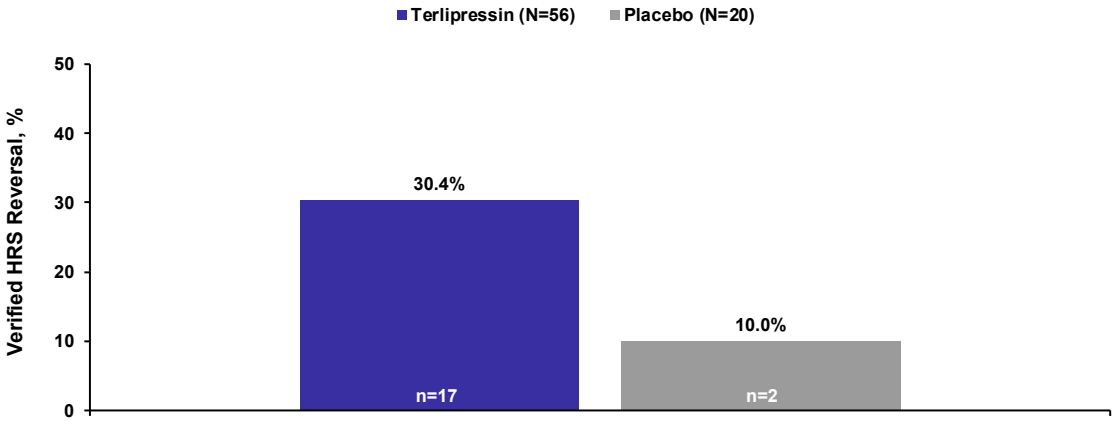
Figure 14. Incidence of RRT Post Liver Transplant in the CONFIRM Study (ITT Population)



ITT, intent-to-treat; RRT, renal replacement therapy.

The incidence of Verified HRS Reversal in transplant-listed subjects was 3 times higher with terlipressin treatment than placebo treatment (Figure 15).

Figure 15. Incidence of Verified HRS Reversal in Transplant-Listed Subjects in the CONFIRM Study (ITT Population)



HRS, Hepatorenal syndrome; ITT, intent-to-treat.

None of the 46 subjects in the terlipressin group who received a transplant died up to Day 90 compared with 2 (6.9%) of 29 placebo subjects who received a transplant.

5.2.8 CONFIRM Efficacy Conclusions

In the CONFIRM study, terlipressin met the prespecified primary endpoint and demonstrated a higher rate of Verified HRS Reversal compared with placebo, a statistically significant difference favoring terlipressin.

Multiple secondary and exploratory endpoints supported the clinical meaningfulness of this finding. Terlipressin treatment led to significantly greater incidence of HRS Reversal in CONFIRM. Improvement in renal function—the hallmark of HRS-1 Reversal—was durable with terlipressin treatment. Terlipressin reduced the incidence of RRT in all HRS-1 subjects and subgroups, including subjects who received liver transplants. Efficacy data from CONFIRM demonstrated improved outcomes among key at-risk subgroups, including subjects with SIRS.

5.3 Study OT-0401

5.3.1 Study Design

OT-0401, a randomized, double-blind, multicenter, placebo-controlled phase 3 study of terlipressin, enrolled 112 subjects with HRS-1 at 35 sites overall in the US (30 sites), Russia (3 sites) and Germany (2 sites). The first subject was enrolled on September 22, 2004, and the last subject completed the 180-day follow-up visit on August 28, 2006. Eligible subjects were randomized in a 1:1 ratio to receive either terlipressin (n=56) or placebo (n=56), stratified by the presence or absence of alcoholic hepatitis. The primary efficacy endpoint was Treatment Success, defined as a SCr decrease to ≤1.5 mg/dL on ≥2 consecutive measurements obtained 48 hours apart, at Day 14. Treatment Success required a SCr measurement on Day 14; for the primary endpoint analysis, missing data were imputed as "not success."

5.3.2 Study Participants

The ITT population consists of the 112 patients randomly assigned to the study (56 patients per treatment group). One subject randomized to placebo did not receive study medication because the subject had spontaneous bacterial peritonitis. More patients in the placebo group received liver transplants prior to Day 14 compared with the terlipressin group, 12 vs 8, respectively.

In the OT-0401 ITT population, 16 (14.3%) subjects received treatment for the maximum 14-day treatment period (11 [19.6%] terlipressin subjects vs 5 [8.9%] placebo subjects). The most common reasons for receiving less than 14 days of treatment included treatment failure (32.1% terlipressin vs 41.1% placebo, with no improvement/RRT for 21% and 38%, respectively); Treatment Success (19.6% vs 10.7%, respectively), and received liver transplant (10.7% vs 8.9%, respectively). The number of subjects alive at each follow-up time point was similar between the treatment groups. No subject was lost to follow-up for the assessment of survival over the 180-day study period.

Demographics and baseline characteristics in the OT-0401 ITT population were comparable between the terlipressin and placebo groups, with the exception of an imbalance in subjects with

SCr >7.0 mg/dL (n=6 for terlipressin vs n=0 placebo). Overall, the subjects in OT-0401 were representative of the general HRS-1 patient population.

5.3.3 Efficacy Results

In the original analysis of the primary endpoint of Treatment Success at Day 14, the incidence in the terlipressin group was double that of placebo but did not attain statistical significance (25.0% for the terlipressin group vs 12.5% for the placebo group; p=0.093 for the ITT population). Logistical issues in collecting data as required for the primary endpoint of Treatment Success at Day 14 in OT-0401 reduced the ability to demonstrate statistical significance. The primary challenge was that the requirement for a SCr value on Day 14 was logistically difficult to collect in subjects who were discharged prior to Day 14 or who only responded on Day 13 or 14, such that collecting the required second SCr value after the first value of ≤1.5 puts their second value outside of the assessment window, automatically labeling them as non-responders.

In agreement with FDA, a re-analysis of the primary efficacy endpoint was performed to include additional post-treatment SCr data that were collected from the existing medical records of subjects who participated in OT-0401. The SCr values were collected according to a specified algorithm that was prospectively agreed to by the FDA, which widened the window for confirmatory SCr to 48 ± 24 hours and allowed substitution of additional Day 13-21 SCr values for missing Day 14 values. The re-analysis showed that 2 additional terlipressin-treated subjects and no placebo-treated subjects met the criteria for Treatment Success so that the total number of patients meeting the requirement for the primary endpoint increased from 14/56 to 16/56. As a result of the agreed-upon re-analysis, the supportive OT-0401 study met its primary endpoint with a significantly higher rate of Treatment Success at Day 14: 28.6% in the terlipressin group compared with 12.5% in the placebo group, with p=0.037.

For the prespecified endpoint of HRS Reversal in the ITT population, which does not have the requirement for the Day 14 value, the incidence of HRS Reversal was significantly higher in terlipressin-treated subjects compared with placebo-treated subjects (33.9 vs 12.5%, nominal p=0.008). The mean time to HRS Reversal was 6.1 days in the terlipressin group vs 3.6 days in the placebo group.

The terlipressin group experienced a substantial reduction in SCr from baseline to Day 14 (-0.7 mg/dL) relative to placebo (0.1 mg/dL) in a repeated measures analysis in the ITT population (secondary endpoint, nominal p=0.002).

5.3.4 Study OT-0401 Conclusions

In the re-analysis based upon additional inclusion of all available post-treatment SCr data, the primary endpoint of incidence of Treatment Success at Day 14 was substantially higher in terlipressin-treated subjects than in placebo-treated subjects (28.6% vs 12.5%, p=0.037). Subjects who received terlipressin had improvements in renal function relative to placebo as

measured by the reversal of HRS-1 and decrease in SCr concentration from baseline through Day 14. These results confirm the favorable results of the CONFIRM study of terlipressin for the treatment of HRS-1, providing supportive evidence of efficacy.

5.4 REVERSE Study

5.4.1 Study Design

REVERSE was a randomized, double-blind, multicenter, placebo-controlled phase 3 study of IV terlipressin in subjects with HRS-1. This study enrolled 196 subjects at 52 sites in the US and Canada. The first subject was enrolled on October 11, 2010, and the last subject completed the 90-day follow-up on May 10, 2013. Subjects were randomized in a 1:1 ratio to receive either terlipressin (n=97) or placebo (n=99), stratified by qualifying SCr (<3.6 mg/dL or ≥3.6 mg/dL) and presence or absence of underlying alcoholic hepatitis. The primary efficacy endpoint was Confirmed HRS Reversal, defined as 2 SCr values ≤1.5 mg/dL at least 48 hours apart while on treatment (a maximum of 24 hours after the last dose of study drug), and without intervening RRT or liver transplant. Based on the experience with OT-0401 and discussions with the FDA, this study eliminated the requirement for a Day 14 SCr value.

All efficacy variables were based on the ITT population, defined as all randomized subjects who had ≥1 baseline assessment. Treatment classification was based on the randomized treatment.

5.4.2 Study Participants

Demographics and baseline characteristics in REVERSE were comparable between the terlipressin and placebo groups for the 196 subjects in the ITT population, with the exception of an imbalance in sex distribution; significantly more female subjects were randomized to the terlipressin group (45/97, 46.4%) compared with the placebo group (32/99, 32.3%; p=0.044). In addition, significantly more subjects in the placebo group had ≥1 LVP within 14 days prior to enrollment (54 [54.6%] placebo subjects vs 36 [37.1%] terlipressin subjects, p=0.0143).

5.4.3 Efficacy Results

Confirmed HRS Reversal in the ITT population was observed in 19/97 (19.6%) subjects in the terlipressin group compared with 13/99 (13.1%) subjects in the placebo group (p=0.2214).

In the ITT population, the number (%) of subjects who achieved HRS Reversal on treatment was 23 (23.7%) subjects in the terlipressin group compared with 15 (15.2%) subjects in the placebo group. The mean time to on-treatment HRS Reversal in terlipressin responders was 6.4 days compared with 7.3 days in the placebo group.

For the prespecified endpoint of least squares mean change in SCr from baseline to EOT, a 0.6 mg/dL greater reduction in SCr was demonstrated with terlipressin (-1.2 mg/dL) than with placebo (-0.6 mg/dL. The number of subjects with >20% improvement in SCr in the terlipressin group (44.3%) was greater than in the placebo group (31.3%).

5.4.4 REVERSE Efficacy Conclusions

The primary endpoint in REVERSE of on-treatment Confirmed HRS Reversal did not reach statistical significance.

The results were directionally supportive of the benefits of terlipressin and consistent with the results observed in other studies in that the primary and secondary endpoint results all favored terlipressin, including Confirmed HRS Reversal and improvements in SCr.

5.5 Efficacy in the Pooled Population

Pooled analyses of all 3 studies provided further assessment of the efficacy and clinical impact of terlipressin in HRS-1. The basis for pooling the 3 placebo-controlled studies was their similar designs, dosing regimens, and patient populations. p-values are not presented for the pooled analyses.

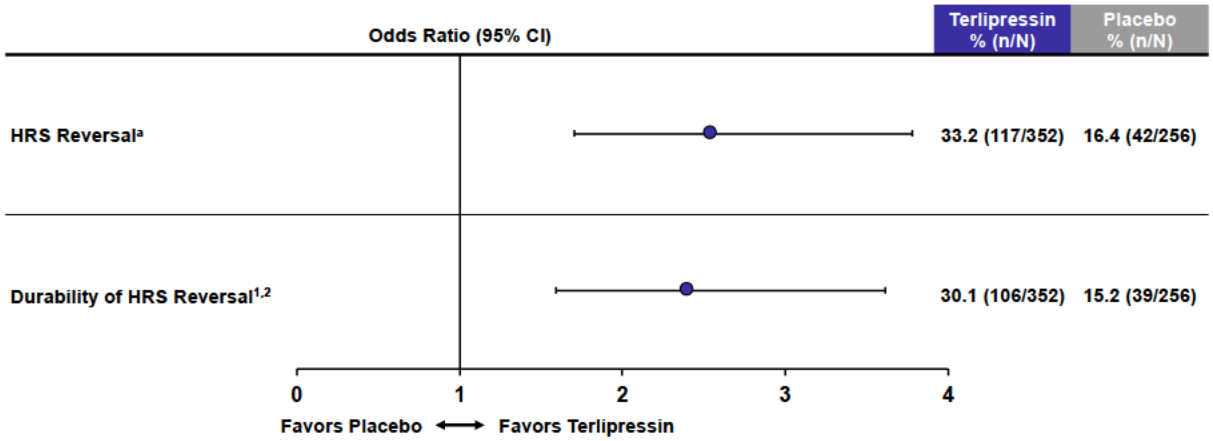
Results of the pooled analyses were consistent with those of the pivotal CONFIRM study. Pooling may allow differences to be seen in the predefined subgroups of patients that are much smaller in the individual studies. The pooled analysis demonstrated that overall survival in the subgroup of transplanted subjects was higher in the terlipressin group compared to the placebo group. Thus, in addition to the clinical benefit of reduced post-transplant RRT already demonstrated in this subgroup in CONFIRM, the pooled analysis showed that terlipressin treatment is associated with a clinically meaningful improvement in survival post liver transplant.

For pooling, none of the primary endpoints could be applied because the studies did not consistently collect the same primary endpoint information. Therefore, HRS Reversal, which was assessed in all the studies, was chosen as the primary endpoint variable for the pooled analyses. HRS Reversal is the standard endpoint in most published studies of HRS-1 and reflects treatment goals in clinical practice and guidelines.

5.5.1 Primary Endpoint: HRS Reversal

For the pooled analysis, HRS Reversal was defined as a SCr value ≤1.5 mg/dL while on treatment up to 24 hours, by Day 14, or discharge, whichever comes first. The incidence of HRS Reversal in terlipressin-treated subjects was twice that in placebo subjects (Figure 16). Likewise, achievement of Durable HRS Reversal, defined as the percentage of subjects with HRS Reversal without RRT to Day 30, with terlipressin was approximately double that with placebo.

Figure 16. HRS Reversal and Durable HRS Reversal in the Pooled Studies (Pooled ITT Population)

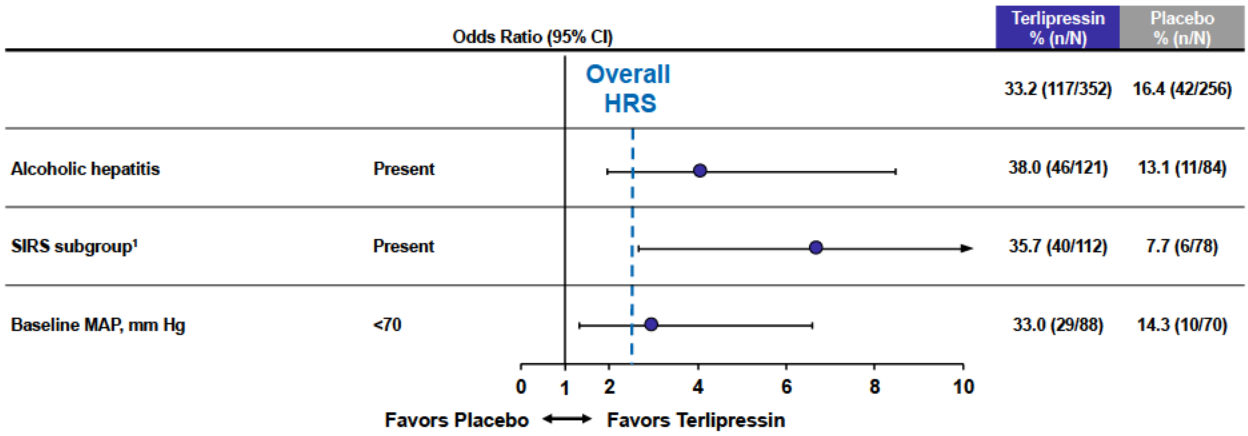


CI, confidence interval; HRS, hepatorenal syndrome; RRT, renal replacement therapy; SCr, serum creatinine.
a. The incidence of HRS Reversal is defined as ≥1 SCr value ≤1.5 mg/dL on treatment (up to 24 hours after the last dose of study medication). Any SCr values obtained post-transplant or RRT are excluded.
b. Defined as the percentage of subjects with HRS Reversal without RRT to Day 30.

5.5.2 Pooled HRS Reversal by Subgroups

The incidence of HRS Reversal was consistently higher in the terlipressin group compared with the placebo group for all subgroups assessed (Appendix Table 49), including the results in the subgroups of baseline alcoholic hepatitis and baseline MAP <70 mm Hg (Figure 17). SIRS status was only collected in the CONFIRM and REVERSE studies. In the SIRS subgroup of the pooled ITT population of these 2 studies, 35.7% of the terlipressin group and 7.7% of the placebo group achieved HRS Reversal.

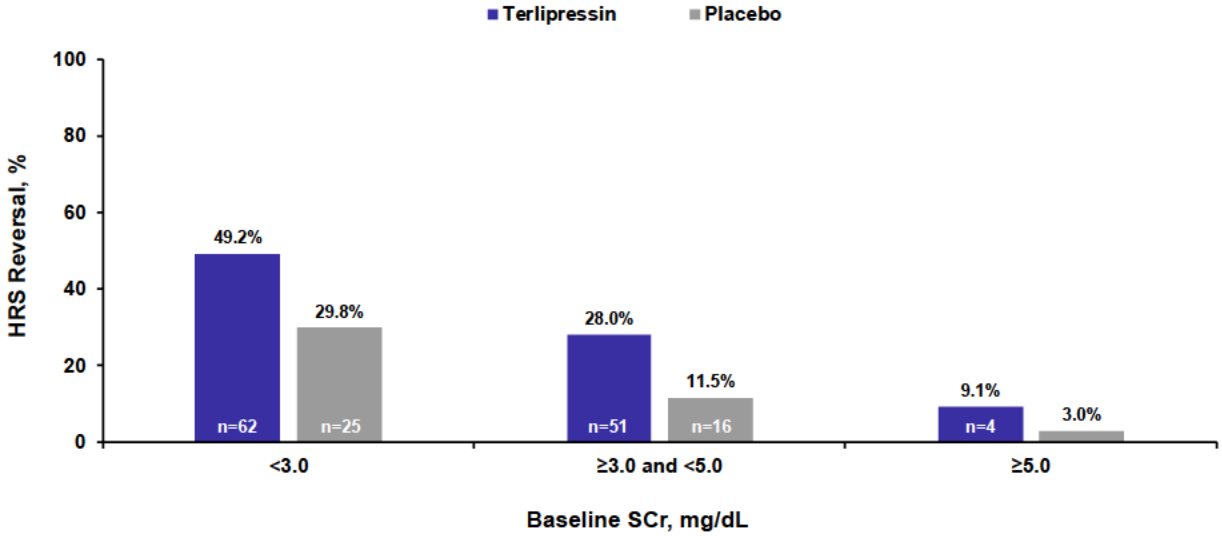
Figure 17. HRS Reversal in High-Risk Subgroups in the Pooled Studies (Pooled ITT Population)



CI, confidence interval; HRS, hepatorenal syndrome; ITT, intent-to-treat; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome.
a. SIRS status only collected in CONFIRM and REVERSE studies.

For all 3 subgroups of baseline SCr, the incidence of HRS Reversal was consistently higher in the terlipressin group (Figure 18).

Figure 18. HRS Reversal by Baseline SCr Levels in the Pooled Studies (Pooled ITT Population)



HRS, hepatorenal syndrome; ITT, intent-to-treat; SCr, serum creatinine.

Upon assessment of the incidence of HRS-1 reversal based on baseline SCr, it became apparent that there may upper limit for baseline SCr above which there is a substantially reduced likelihood of achieving HRS-1 reversal. In our studies, the maximum baseline SCr value recorded for subjects who ultimately achieved HRS-1 reversal was between 5.2 mg/dL and 6.2 mg/dL in the terlipressin group and 4.3 to 5.2 mg/dL in the placebo group (based on the study; Table 18), suggesting an overall higher threshold for response with terlipressin but a differing likelihood of response based on severity of the kidney dysfunction at baseline.

Table 18: Maximum Baseline SCr for Subjects who Achieved HRS-1 Reversal (by Study)

	CONFIRM		OT-0401		REVERSE	
	Terlipressin	**Placebo**	**Terlipressin**	**Placebo**	**Terlipressin**	**Placebo**
Maximum Baseline SCr (mg/dL)	5.2	4.3	5.6	4.7	6.2	5.2

Therefore, in an effort to optimize the benefit risk for patients who will be treated with terlipressin, we have evaluated the relationship of baseline SCr on HRS reversal and the benefits and risks of terlipressin in subgroups of patients with a baseline of <5 mg/dL and ≥5 mg/dL. A SCr ≥ 5 mg/dL is the value used to define the highest grade of kidney failure within the CLIF-SOFA score.

As described (Figure 18), the incidence of HRS-1 reversal is consistently higher with terlipressin compared with placebo in all baseline SCr sub-groups evaluated. However, in both treatment groups, subjects with a baseline SCr ≥5 g/dL have a lower incidence of HRS-1 reversal than subjects with a SCr <5 mg/dL. Specifically, in the sub-group of subjects with baseline SCr ≥5 mg/dL, the incidence of HRS-1 reversal is 9.1% in the terlipressin compared to 3.0% in the placebo group; these proportions are substantially lower than for subjects with a baseline SCr <5 mg/dL. The same pattern of results were seen in the pivotal CONFIRM study.

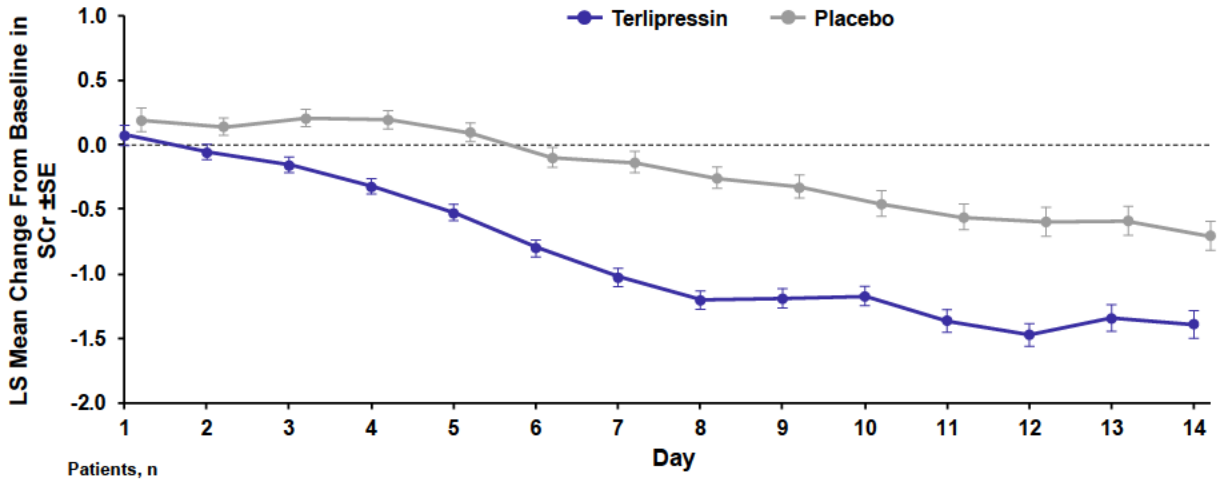
Identification of patients most likely to benefit from terlipressin treatment and how the benefit-risk of terlipressin can be optimized based on baseline SCr is described in detail in Section 8.1.

5.5.3 Change From Baseline Through EOT in Renal Function

The repeated measures analysis results of the change in SCr level from baseline through EOT with interaction between treatment and day for the pooled studies found that SCr reductions from baseline to EOT were significantly greater in the terlipressin group than in the placebo group (Figure 19). The LS mean treatment difference from baseline to EOT between the terlipressin and placebo groups was 0.6 mg/dL. Without the interaction, the treatment difference was

0.5 mg/dL. Note that baseline is defined as the last value prior to the start of study medication. Most baseline values are from Day 1, resulting in fewer change from baseline values for Day 1.

Figure 19. Repeated Measures Analysis of Mean Change From Baseline in SCr by Day in the Pooled Studies (Pooled ITT Population)



Patients, n														
Terlipressin	91	330	298	263	215	169	132	105	97	75	59	48	36	33
Placebo	64	237	224	191	147	113	98	83	64	50	40	30	28	25

ITT, intent-to-treat; LS, least squares; RRT, renal replacement therapy; SCr, serum creatinine; SE, standard error.
SCr values after RRT and liver transplant are excluded. Only SCr values collected after the treatment start date through 24 hours after the treatment end date are included.
Baseline is defined as the last value prior to the start of study medication. Most baseline values are from Day 1, resulting in fewer change from baseline values for Day 1.

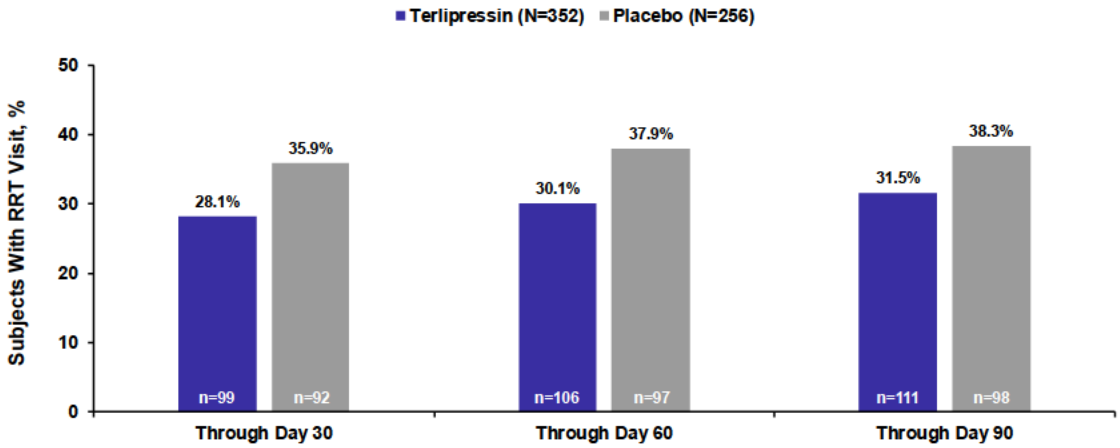
5.5.4 Greater Than 30% Improvement in SCr From Baseline to EOT

In the pooled analysis, 42.9% of terlipressin subjects compared with 23.4% of placebo subjects achieved a >30% improvement in SCr from baseline to EOT.

5.5.5 Cumulative Incidence of RRT Through Day 90

In the pooled analysis, terlipressin reduced the incidence of RRT through Day 30, Day 60, and Day 90 compared with placebo (Figure 20).

Figure 20. Incidence of RRT Through Day 90 in the Pooled Studies (Pooled ITT Population)

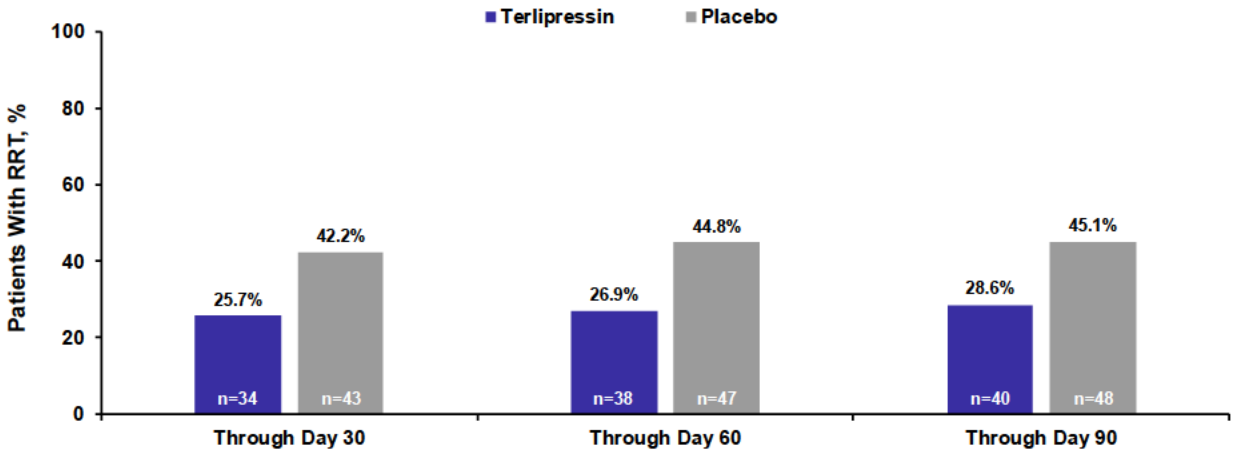


ITT, intent-to-treat; RRT, renal replacement therapy.
For OT-0401 and CONFIRM, dates/times were used to determine 30, 60, and 90 days. For REVERSE, RRT was recorded at the visits for Days 30, 60, and 90 without an RRT date.

5.5.6 Incidence of RRT Through Day 90 in Subjects Alive

A greater percentage of living subjects at Day 90 without incidence of RRT was observed in the terlipressin group (36.9%) compared with the placebo group (28.5%). This finding corresponds to the substantially greater improvement in renal function seen with terlipressin (Figure 21).

Figure 21. Incidence of RRT in Subjects Alive Through Day 90 in the Pooled Studies (Pooled ITT Population)



ITT, intent-to-treat; RRT, renal replacement therapy.
REVERSE only captures yes/no if there was an RRT by these follow-up days. This information is used instead of the study day.

5.5.7 Key Clinical Outcomes in Liver Transplant Recipients

Liver transplant is the only curative treatment for the underlying liver disease in patients with HRS-1 and patients who are transplanted can live for decades. Therefore, optimizing outcomes in the peri-transplant period is important to afford patients the longest possible survival.

5.5.7.1 Subjects Listed for Liver Transplant at Baseline in CONFIRM and REVERSE

Transplant list status was not collected in OT-0401. In REVERSE and CONFIRM, not every subject listed for a transplant received one by Day 90 (Table 19). A similar proportion of patients died before receiving a transplant and were alive without receiving a transplant between the terlipressin and placebo groups of subjects listed for transplant.

Table 19. Transplant Status, Died by Day 90, and Alive Without Transplant by Day 90 for Subjects Listed for Transplant at Baseline in the REVERSE and CONFIRM Pooled Studies (Pooled ITT Population)

	REVERSE and CONFIRM	
	Terlipressin N=92 n (%)	**Placebo N=59 n (%)**
Received a transplant by Day 90	58 (63.0)	42 (71.2)
Died without transplant by Day 90	21 (22.8)	12 (20.3)
Alive without transplant by Day 90	14 (15.2)	9 (15.3)

ITT, intent-to-treat; N, number of subjects in the treatment group; n, number of subjects in the category in the treatment group.
In REVERSE, 1 subject in the terlipressin group and 3 subjects in the placebo group who received transplants died.
In CONFIRM, 1 subject in the placebo group who received a transplant died.

5.5.7.2 Incidence and Time to Transplantation for Transplant Subjects by Day 90 in the Individual Studies

Across studies, 26.7% of subjects in the terlipressin and 30.5% in the placebo group underwent a liver transplant by Day 90. A slightly lower transplant rate was observed in CONFIRM in both treatment groups compared with OT-0401 and REVERSE (Table 20).

In the CONFIRM study, 23.1% of the subjects in the terlipressin group received a liver transplant by Day 90 and 28.7% in the placebo group, representing a difference of 5.6 percentage points. It's difficult to determine the exact reasons for the lower rate of transplantation on terlipressin in CONFIRM as the study was not designed to evaluate the factors influencing liver transplantation. This finding was not replicated in the other 2 studies where rates of transplantation were similar between treatment arms. There are 3 possible major factors, either alone or in combination, that may explain the difference in CONFIRM. First, an improvement of renal function on terlipressin could have caused a decrease in MELD score, resulting in a lower prioritization on the transplant list. Second, terlipressin could have caused an AE that delayed or prevented transplantation. Third, the difference could have occurred by chance and factors unrelated to treatment, since the randomization did not account for factors that could have influenced transplantation, such as blood type, geographic region (UNOS region).

Additionally, the slightly lower transplant rate in CONFIRM may be due to the higher rate of subjects with alcoholic hepatitis than in the other 2 studies. Patients with alcoholic hepatitis are often not initially considered candidates for liver transplant, but they may become so with recovery from alcoholic hepatitis and improvement in their ACLF stage. In CONFIRM and OT-0401, mean time to transplantation was longer in the terlipressin group than in the placebo

group, while in REVERSE, the mean time to transplant was similar between treatment groups. Mean time to transplant was not calculated for the pooled data.

Table 20. Incidence and Time to Transplantation for Transplant Subjects by Day 90 in the Individual Studies (ITT Population)

	CONFIRM		OT-0401		REVERSE	
	Terlipressin N=199	Placebo N=101	Terlipressin N=56	Placebo N=56	Terlipressin N=97	Placebo N=99
Subjects receiving transplant by Day 90						
n (%)	46 (23.1)	29 (28.7)	18 (32.1)	17 (30.4)	30 (30.9)	32 (32.3)
Time to transplantation by Day 90, days						
Mean (SD)	24.6 (23.47)	21.5 (19.33)	28.3 (29.0)	19.6 (22.9)	16.6 (22.02)	17.6 (20.61)
Median	17.0	13.0	18.5	11.0	5.6	11.2
Min, max	2.0, 122.0	2.0, 71.0	0.0, 90.0	4.0, 82.0	0.1, 88.4	0.6, 80.9

ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SD, standard deviation.

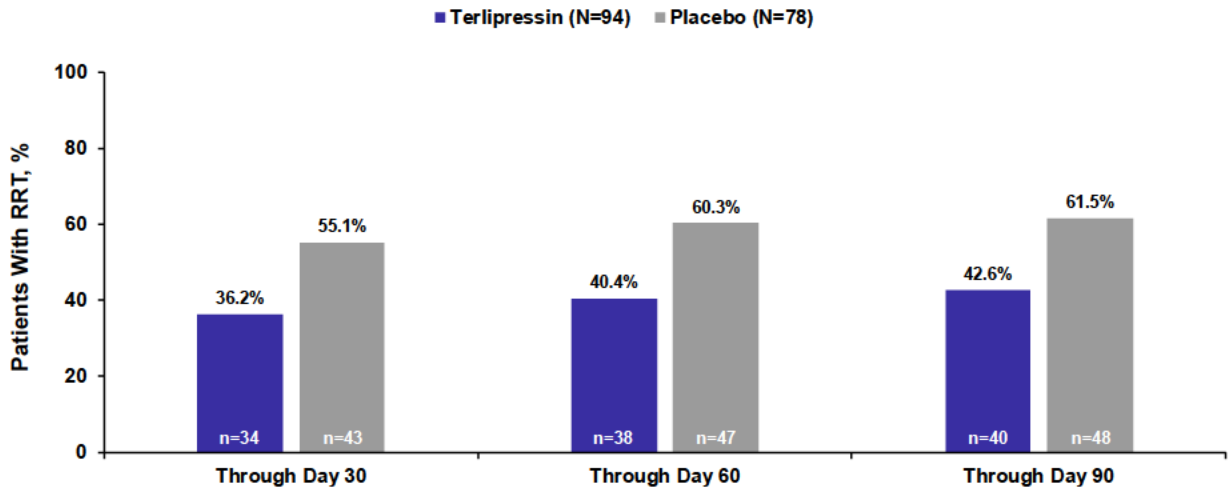
5.5.7.3 HRS Reversal for Liver Transplant Subjects

A greater proportion of subjects who received a liver transplant in the terlipressin group (28.7%, n=27 of 94 subjects) achieved HRS Reversal than in the placebo group (12.8%, n=10 of 78 subjects).

5.5.7.4 RRT in Liver Transplant Subjects Through Day 90

In the terlipressin group, there was a lower incidence of RRT in transplanted subjects at each time point assessed and the difference between treatment groups was consistently approximately 20 percentage points lower in the terlipressin group at all time points (Figure 22). The importance of this finding is that renal failure requiring RRT post liver transplant is a major risk factor for graft dysfunction and death in liver transplant recipients.

Figure 22. Incidence of RRT in Transplant Subjects Through Day 90 in the Pooled Studies (Pooled ITT Population)



ITT, intent-to-treat; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; RRT, renal replacement therapy.
For OT-0401 and CONFIRM, dates/times were used to determine 30, 60, and 90 days. For REVERSE, RRT was recorded at the visits for days 30, 60, and 90 without an RRT date.

5.5.7.5 Overall Survival in Post Liver Transplant Subjects

Based on the FDA feedback during the pre-NDA meeting in October 2019 and subsequent communications, the sponsor performed post hoc analyses to understand trends on clinical benefits of restoring renal function in transplanted subjects across the 3 studies. Terlipressin treatment led to a higher rate of HRS Reversal and a lower incidence of RRT in subjects who received a liver transplant across the phase 3 studies. This was associated with lower post-transplant RRT and better overall survival in terlipressin-treated subjects who received a liver transplant. Nominal p-value for this post hoc analysis is 0.014 (Figure 23, Table 21).

Figure 23. Overall Survival for Transplanted Subjects at 90 Days in the Pooled Studies (Pooled ITT Population)

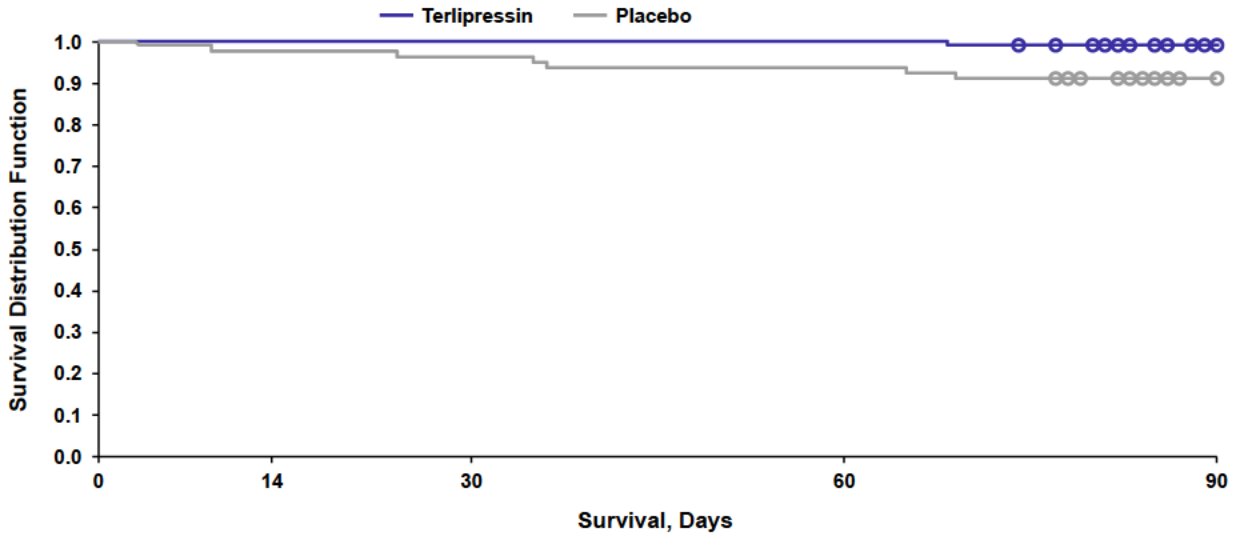


Table 21. Overall Survival up to Day 90 for Transplanted Subjects in the Pooled Studies (Pooled ITT Population)

	Terlipressin		Placebo	
Overall Survival up to 90 Days	**N**	**Parameter**	**N**	**Parameter**
Survival estimate	94	0.989	78	0.910
Alive at Day 90 (n, %)	94	93 (98.9)	78	71 (91.0)

ITT, intent-to-treat; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group.

5.5.8 Evidence of Efficacy in the Literature

Terlipressin has been the most extensively studied treatment of HRS-1 and substantial literature provide supportive evidence for the efficacy of terlipressin in the treatment of HRS-1. The results of the CONFIRM, OT-0401, and REVERSE studies are consistent with the literature, demonstrating that terlipressin improves renal function in subjects with HRS.

More than 40 published studies show the effects of terlipressin on improving renal function in HRS-1 patients.

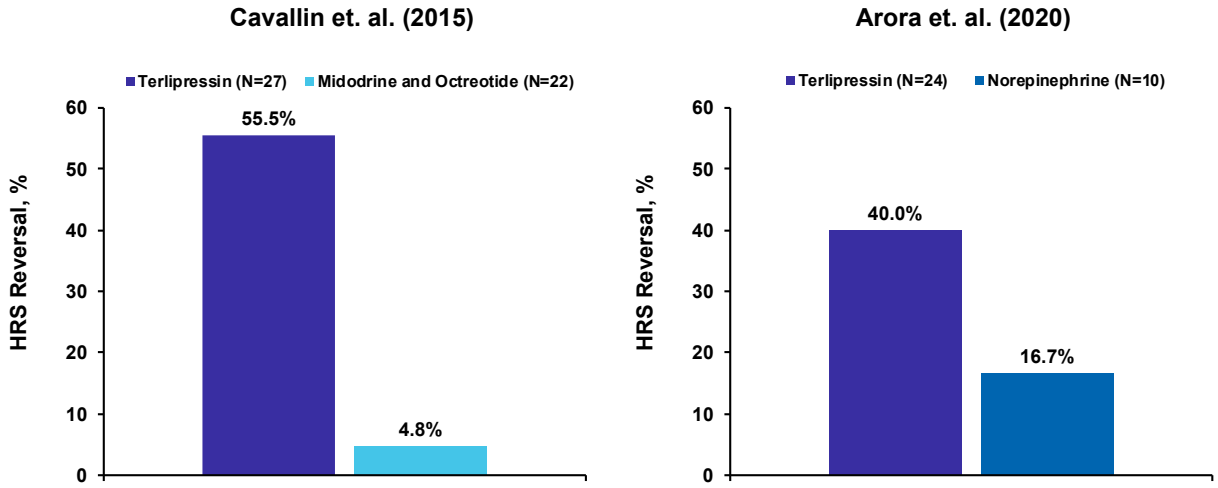
The combination of midodrine and octreotide is the most commonly used off-label therapy for treatment of HRS-1 in the US. Yet very little data exists from randomized prospective studies for

this drug combination. In the only randomized controlled study to date, terlipressin was significantly more effective at achieving HRS Reversal than midodrine and octreotide (p<0.001; Cavallin 2015; Figure 24). While the precise effectiveness of terlipressin versus norepinephrine remains unclear, based on the most recent and largest study comparing terlipressin with norepinephrine, the proportion of subjects achieving HRS Reversal was significantly higher with terlipressin (p=0.004; Figure 24; Arora 2020). In addition, a significant reduction in the requirement for RRT (56.6% vs 80%, p=0.006) and improved 28-day survival (48.3% vs 20%, p=0.001) were observed in this study.

A meta-analysis (Zheng 2017) suggests that terlipressin is superior to norepinephrine and other vasoconstrictors for HRS Reversal.

Taken as a whole, the published literature supports the increased effectiveness of terlipressin plus albumin in reversing HRS-1 when compared to other treatments.

Figure 24. HRS Reversal With Terlipressin Versus Other Vasoconstrictors



HRS, hepatorenal syndrome; N, number of subjects in the treatment group.
Cavallin M, et al. *Hepatology* 2015;62:567-74; Arora V, et al. *Hepatology* 2020;71:600-10.

5.5.9 Terlipressin Efficacy Conclusions

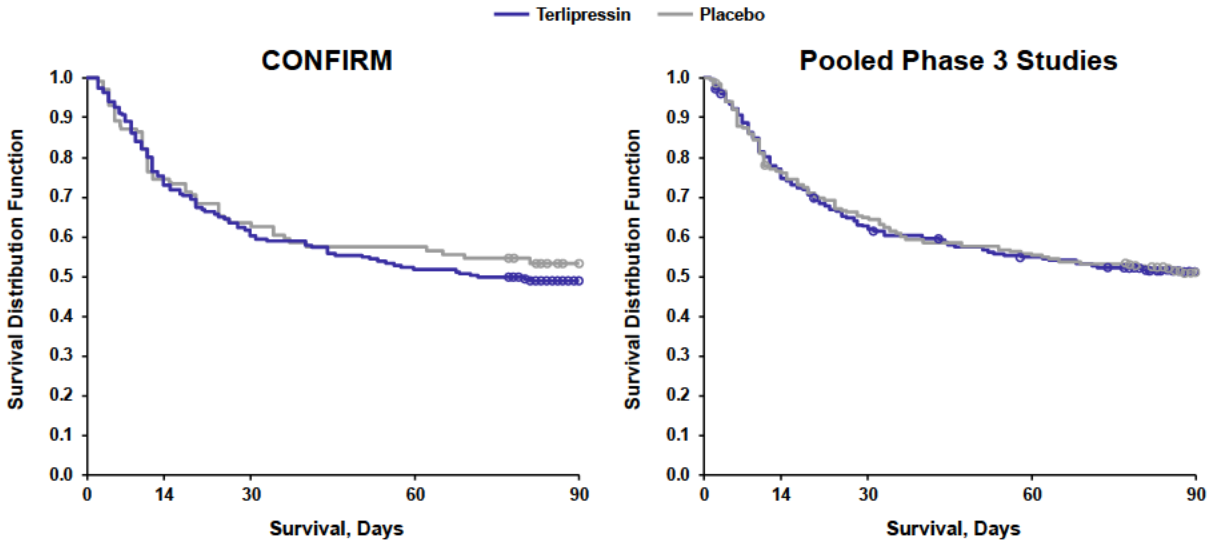
The results of the pivotal phase 3 CONFIRM study, the re-analysis of the supportive phase 3 efficacy OT-0401 study, and the pooled analysis of all 3 studies show that terlipressin treatment is superior to placebo for achieving durable reversal of HRS-1 and improvement of renal function. A review of recent literature supports that terlipressin is effective therapy for HRS-1.

In these CONFIRM and OT-0401 studies and the pooled analysis of all 3 studies, terlipressin treatment is associated with additional clinical benefits, including decreased incidence of RRT and decreased length of ICU stay. In subjects receiving a liver transplant, terlipressin improves clinical outcome compared with placebo, including a substantially lower incidence of RRT post-transplant. Finally, terlipressin is particularly effective at reversing HRS in the high-risk subgroups of subjects with alcoholic hepatitis, SIRS, or low baseline MAP.

6 OTHER OUTCOMES

Overall survival in CONFIRM and the pooled phase 3 studies was similar between the treatment groups in CONFIRM (51.7% for terlipressin, 52.0% for placebo) and in the pooled analyses (Figure 25).

Figure 25. Overall Survival Up to 90 Days in CONFIRM and the Pooled Phase 3 Studies



Although overall survival was numerically slightly lower in the terlipressin group versus the placebo group in CONFIRM, this must be interpreted in the context of survival without transplant (ie, alive at any time without transplant; terlipressin 26.1% vs placebo 26.7%). The numerical difference in overall survival up to Day 90 between the terlipressin and placebo groups, 4.8%, may have been influenced by the lower rate of transplant in the terlipressin group compared with the placebo group (23.1% vs 28.7%, respectively). Liver transplantation is the definitive treatment for advanced decompensated cirrhosis, however, not all patients are candidates for liver transplantation. Challenges to patients receiving a liver transplant include the complex system for being listed for an organ transplant, the process of being prioritized for transplant, complications that occur while on the waiting list that can lead to delisting, and availability of a donor organ.

Terlipressin is an acute short-term treatment for a single complication of advanced progressive liver disease. While terlipressin significantly improves renal function and reverses HRS-1, it does not treat the underlying decompensated cirrhosis. HRS-1 is only 1 aspect of a complex interplay of multiple simultaneous and sequential organ dysfunctions occurring in the setting of advanced decompensated cirrhosis. In addition to HRS-1, patients frequently have concomitant

conditions that include infection, sepsis, hepatic encephalopathy, coagulopathy, pulmonary dysfunction, and variceal bleeding. This is further supported by literature; a random-effects model meta-analysis (Gluud 2012) found that terlipressin reduced mortality (RR 0.76, 95% CI 0.61 to 0.95), but the impracticality around large sample size trials makes it impossible to demonstrate this mortality effect in a single clinical trial. Sample size for a study to show statistical significance based on a 5% difference in survival estimate powered at 80% would require >3000 patients, which is impractical in this rare condition.

Hence, the goal of treatment of HRS-1 is to reverse the functional renal failure and bring the condition back from a decompensated cirrhosis to a compensated state. Without liver transplant, mortality at 90 days is predicted by baseline disease state severity (ie, MELD score). Based on a baseline MELD of 33 as reported for the CONFIRM study, predicted 90-day mortality is >70% in patients with cirrhosis and alcoholic hepatitis (Mayo Clinic 2020). Moreover, ACLF grades 2 or 3 – indicative of severely decompensated cirrhosis – predict survival more accurately than treatment response (Angeli 2015b). More than half of the subjects enrolled in CONFIRM had ACLF-2 or worse. Piano (2018) assessed several European cohorts of HRS-1 patients treated with terlipressin and albumin and found that ACLF-3 predicted mortality regardless of terlipressin response.

For these reasons, overall survival was not assessed as a primary or secondary endpoint in CONFIRM, and no overall survival benefit was seen.

While no overall survival benefit is seen in CONFIRM or the pooled studies when all data are assessed, analysis of survival based on baseline SCr as an indicator of severity of disease, shows that overall survival is substantially decreased with terlipressin compared with placebo (ie, albumin alone) in subjects with the most advanced renal dysfunction (ie baseline SCr ≥5 mg/dL) in both CONFIRM and the pooled studies. As previously described, these highly compromised patients are less likely to experience HRS-1 reversal. Therefore the use of terlipressin is not recommended in patients with the most advanced renal dysfunction.

Figure 26: Overall Survival up to 90 Days by Treatment Group and Baseline SCr (Pooled Studies; Intent-to-treat Population)

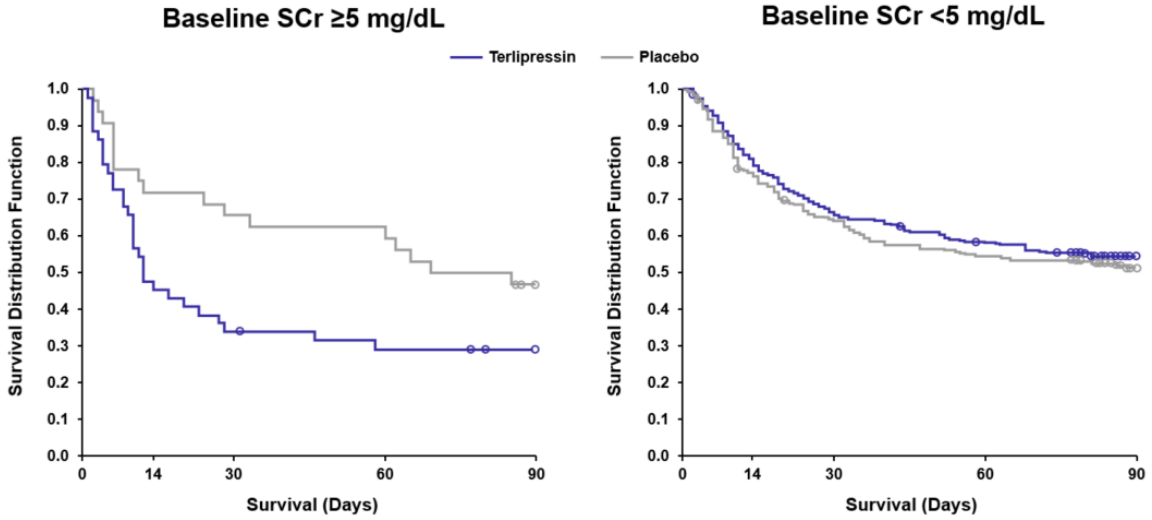
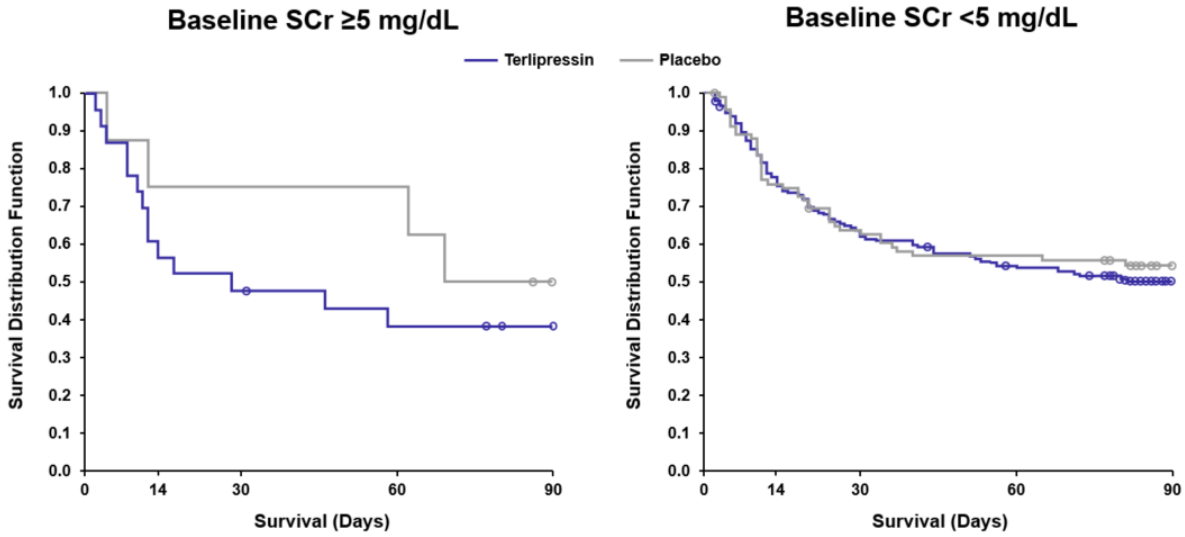


Figure 27: Overall Survival up to 90 Days by Treatment Group in Subjects with Baseline SCr ≥ 5 mg/dL (CONFIRM; Intent-to-treat Population)



7 SAFETY

The safety profile of terlipressin is well characterized, with the majority of AEs being predictable, recognizable, and generally manageable in the hospital setting where HRS-1 patients are treated. Most of the events observed in company-sponsored clinical studies were expected based on terlipressin's V_1-receptor activity and were consistent with the known post-marketing experience with terlipressin outside the US.

7.1 Safety in the Phase 3 Clinical Studies of Terlipressin for HRS-1

The terlipressin clinical development program is the largest ever undertaken for HRS-1. CONFIRM, OT-0401, and REVERSE were double-blind, placebo-controlled clinical studies in HRS-1 that had similar inclusion/exclusion criteria, study designs, and dosing regimens; therefore, safety data for all subjects treated with study drug are pooled and integrated for all safety data presentations. Overall, 349 subjects with HRS-1were treated with terlipressin and 249 were treated with placebo (Table 22). In the integrated safety population of the 3 studies, these 349 subjects received an average daily terlipressin dose of 3.6 mg for a mean duration of 6.2 days and a maximum duration of 25 days.

Table 22. Subject Distribution in the Integrated and Individual Phase 3 Studies

	Terlipressin	Placebo
Integrated phase 3 studies, n	349	249
CONFIRM	200	99
OT-0401	56	55
REVERSE	93	95

7.1.1 Adverse Event Assessments

All AEs were assessed by the investigator and recorded starting with the first administration of study drug (treatment-emergent) until 7 days after discontinuation of study drug, except SAEs, which were assessed by the investigator and recorded until 30 days after discontinuation of study drug (Table 23). In OT-0401, all deaths during the 180-day follow-up were recorded as SAEs. As agreed with the FDA, REVERSE and CONFIRM followed subjects until Day 90; all deaths during the 90-day follow-up were recorded as SAEs.

Table 23. Adverse Event Assessments in CONFIRM, OT-0401, and REVERSE

AE Type	CONFIRM	OT-0401	REVERSE
AE	Recorded up to 7 days after discontinuation of treatment (captured in the clinical database)		
SAE	Recorded up to 30 days after discontinuation of treatment (captured in the clinical database and global company pharmacovigilance database [Argus])		
Death	Recorded up to 90 days from the start of study drug (captured in the clinical database)	Recorded up to 180 days from the start of study drug (captured in the clinical and global company pharmacovigilance database [Argus])	Recorded up to 90 days from the start of study drug (captured in the clinical and global company pharmacovigilance database [Argus])

AE, adverse event; SAE, serious adverse event.

7.2 Safety Analyses Results

7.2.1 Safety Population

The safety population for the integrated analysis of the safety data was defined as all subjects randomized to treatment who received ≥1 dose of study drug in CONFIRM, OT-0401, or REVERSE (N=349), rather than all subjects randomized to treatment (ITT, N=352). For the 12 subjects (n=6 CONFIRM, n=2 OT-0401, and n=4 REVERSE) who were retreated after their initial treatment period, the summaries of exposure, concomitant medications, and AEs combine the initial and retreatment periods in the integrated analyses.

7.2.2 Exposure to Terlipressin

In all 3 studies, the starting dose of terlipressin acetate was 4 mg/day (1 mg q6h; equivalent to 0.85 mg of terlipressin q6h) administered IV as a bolus injection over 2 minutes. In CONFIRM and REVERSE, the dose could be increased from 1 mg to 2 mg q6h (8 mg/day) on Day 4 if SCr had not decreased by ≤30%. The CONFIRM and REVERSE protocols required subjects to discontinue study treatment on Day 4 (minimum of 10 doses) if their SCr value was greater than or equal to baseline. OT-0401 required discontinuation on Day 7 for SCr values greater than or equal to baseline.

In CONFIRM, OT-0401, and REVERSE, a total of 349 subjects received terlipressin and 249 subjects received placebo. In the integrated analysis, mean durations of dosing, exposure, and total number of doses were similar for terlipressin- and placebo-treated subjects (Table 24). The majority of subjects received a standard 1-mg dose of terlipressin; 95 subjects (27.2%) received a high dose of terlipressin, defined as ≥1 dose of 2 mg.

Table 24. Exposure to Treatment in the Integrated Phase 3 Studies (Safety Population)

Parameter		Integrated Phase 3 Studies	
		Terlipressin N=349	**Placebo N=249**
Duration,[a,b] (days)	N	349	249
	Mean (SD)	6.2 (4.39)	6.0 (3.86)
	Median	5.0	4.0
	Minimum, maximum	1.0, 25.0	1.0, 19.0
Duration range, n (%)	≤3 days	95 (27.2)	67 (26.9)
	>3 and ≤6 days	131 (37.5)	92 (36.9)
	>6 and ≤9 days	54 (15.5)	47 (18.9)
	>9 and ≤12 days	30 (8.6)	15 (6.0)
	>12 days	39 (11.2)	28 (11.2)
Total number of doses of exposure[a]	N	349	249
	Mean (SD)	21.1 (17.18)	20.5 (15.36)
	Median	15.0	13.0
	Minimum, maximum	1.0, 92.0	1.0, 68.0
Range of total number of doses of exposure[a], n (%)	≤10 doses	99 (28.4)	69 (27.7)
	>10 doses	250 (71.6)	180 (72.3)
Total exposure[a], mg	N	349	249
	Mean (SD)	26.6 (27.44)	27.4 (26.12)
	Median	15.0	13.0
	Minimum, maximum	1.0, 153.0	1.0, 121.0
Daily exposure, mg/day	N	349	249
	Mean (SD)	3.6 (1.39)	3.8 (1.46)
	Median	3.2	3.3
	Minimum, maximum	0.8, 7.2	1.0, 8.6
Dose level,[a,c] n (%)	Standard	254 (72.8)	163 (65.5)
	High	95 (27.2)	86 (34.5)
Total number of doses ≥2 mg	N	95	86
	Mean (SD)	21.7 (15.14)	19.9 (12.72)
	Median	18.0	16.0
	Minimum, maximum	1.0, 66.0	1.0, 46.0

N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SD, standard deviation.

a. For subjects receiving initial and retreatment periods, exposure data are combined from both periods.

b. The number of days the subject received at least 1 dose of study drug is counted. For the combination of initial and retreatment periods, the counts from each period are added together.

c. Subjects in the standard dose level received only 0.5- and 1-mg doses. Subjects in the high dose level received at least 1 dose of 2 mg.

7.2.3 Concomitant Albumin Use

In keeping with standard medical practice and current treatment guidelines at the time of the studies, concomitant albumin administration was strongly recommended for all subjects in these studies. In the integrated analysis, concomitant albumin use was 86% in the terlipressin group and 92% for the placebo group during the treatment period, and the mean total exposures were 217.7 g and 243.0 g, respectively.

7.2.4 Concomitant Medications of Interest

Nearly all subjects took 1 or more concomitant medications during study treatment. Drugs for the treatment of alcoholic hepatitis were used at a similar frequency in the integrated terlipressin- and placebo-treated groups (Table 25). Diuretics and drugs for obstructive airway diseases were used more frequently by terlipressin-treated subjects than by placebo-treated subjects, likely due to the increased occurrence of respiratory AEs and potential fluid overload in terlipressin-treated subjects.

Table 25. Concomitant Medications of Interest in the Integrated Phase 3 Studies (Safety Population)

Concomitant Medication	Integrated Phase 3 Studies	
	Terlipressin N=349	Placebo N=249
Treatment for alcoholic hepatitis	43 (12.3)	33 (13.3)
Antibiotics	136 (39.0)	101 (40.6)
Anti-infectives for systemic use	159 (45.6)	128 (51.4)
Beta blocking agents	54 (15.5)	51 (20.5)
Diuretics	94 (26.9)	44 (17.7)
Obstructive airway disease drugs	64 (18.3)	21 (8.4)

N, number of subjects in the treatment group.

7.2.5 Demographic and Baseline Characteristics

The OT-0401 inclusion and exclusion criteria were based on the original 1996 ICA guidelines; CONFIRM and REVERSE inclusion and exclusion criteria were based on the then-current HRS-1 diagnosis criteria (Salerno 2007), resulting in a patient population with advanced disease, typical of patients with HRS-1, many of whom had high MELD scores, high CLIF-SOFA scores, an advanced stage of ACLF, and high predicted mortality. All subjects had to have both a rapidly progressive reduction in renal function and no sustained improvement in renal function in the diagnostic fluid challenge as defined in Table 5.

In the integrated studies, the demographic and baseline characteristics were similar between treatment groups (Table 26).

Table 26. Demographic and Baseline Characteristics in the Integrated Phase 3 Studies (Safety Population)

Parameter	Integrated Phase 3 Studies	
	Terlipressin N=349	**Placebo N=249**
Age, years		
n	349	249
Mean (SD)	54.0 (10.62)	54.1 (10.50)
Median	55.2	55.5
Minimum, maximum	23.2, 78.0	25.4, 81.6
Weight, kg		
n	333	236
Mean (SD)	89.2 (25.64)	85.9 (22.98)
Median	85.0	80.0
Minimum, maximum	41.0, 241.0	42.0, 164.0
Sex, n (%)		
Male	211 (60.5)	160 (64.3)
Female	138 (39.5)	89 (35.7)
Ethnicity, n (%)		
Hispanic or Latino	45 (12.9)	37 (14.9)
Not Hispanic or Latino	301 (86.2)	212 (85.1)
Race, n (%)		
American Indian or Alaskan Native	3 (0.9)	4 (1.6)
Asian	8 (2.3)	1 (0.4)
Black or African American	24 (6.9)	14 (5.6)
Native Hawaiian or another Pacific Islander	0	1 (0.4)
White	310 (88.8)	228 (91.6)
Geographic region, n (%)		
United States	310 (88.8)	222 (89.2)
Non-United States	39 (11.2)	27 (10.8)

N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SD, standard deviation.

Mean values at baseline for SCr, MELD score, encephalopathy score, bilirubin, and MAP were similar between treatment groups in the integrated data (Table 27). The proportion of subjects with MAP values <70 mm Hg was also similar between treatment groups.

Table 27. Baseline Disease Characteristics in the Integrated Phase 3 Studies (Safety Population)

Parameter	Integrated Phase 3 Studies	
	Terlipressin N=349	**Placebo N=249**
Alcoholic Hepatitis, n (%)		
Present	121 (34.7)	82 (32.9)
Not Present	228 (65.3)	167 (67.1)
Baseline SCr, mg/dL		
n	349	249
Mean (SD)	3.6 (1.29)	3.6 (1.09)
Median	3.3	3.4
Minimum, maximum	1.9, 11.9	1.6, 6.9
Baseline MELD score		
n	311	217
Mean (SD)	33.0 (6.38)	33.1 (5.84)
Median	34.0	34.0
Minimum, maximum	16.0, 40.0	17.0, 40.0
Baseline Child-Pugh-Turcotte score, n (%)		
Class A (5-6)	5 (1.4)	3 (1.2)
Class B (7-9)	101 (28.9)	69 (27.7)
Class C (10-5)	229 (65.6)	163 (65.5)
Missing	14 (4.0)	14 (5.6)
Baseline encephalopathy score		
n	345	244
Mean (SD)	0.9 (0.96)	1.0 (0.97)
Median	1.0	1.0
Minimum, maximum	0.0, 3.0	0.0, 4.0
Baseline bilirubin, mg/dL		
n	335	242
Mean (SD)	12.9 (12.84)	14.0 (14.53)
Median	7.0	6.8
Minimum, maximum	0.3, 51.6	0.7, 98.0
Baseline MAP		
n	349	249
Mean (SD)	77.4 (11.91)	76.8 (10.90)
Median	76.3	76.0
Minimum, maximum	47.0, 117.7	51.7, 117.3

Table 27. Baseline Disease Characteristics in the Integrated Phase 3 Studies (Safety Population)

Parameter	Integrated Phase 3 Studies	
	Terlipressin N=349	**Placebo N=249**
Baseline MAP <65 mm Hg, n (%)	48 (13.8)	32 (12.9)
Baseline MAP <70 mm Hg, n (%)[b]	N=352	N=256
	88 (25.0)	70 (27.3)
SIRS subgroup,[a] n (%)	N=293	N=194
	110 (37.5)	77 (39.7)

ITT, intent-to-treat; MAP, mean arterial pressure; MELD, model for end-stage liver disease; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

a. In CONFIRM and REVERSE studies only.

b. Intent-to treat population.

The most common cause of cirrhosis was alcohol use in the integrated studies, with a similar percentage in each treatment group (Table 28). Slightly more than half of the subjects presented with esophageal varices.

Table 28. Hepatic History in the Integrated Phase 3 Studies (Safety Population)

Parameter	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	**Placebo N=249 n (%)**
Cirrhosis cause		
Alcohol	211 (60.5)	146 (58.6)
Hepatitis B	10 (2.9)	5 (2.0)
Hepatitis C	87 (24.9)	67 (26.9)
Primary biliary cirrhosis	11 (3.2)	7 (2.8)
Hepatocellular carcinoma	23 (6.6)	24 (9.6)
Autoimmune hepatitis	14 (4.0)	8 (3.2)
Nonalcoholic steatohepatitis	52 (14.9)	35 (14.1)
Esophageal varices	185 (53.0)	135 (54.2)
If yes, prior history?	47 (13.5)	45 (18.1)
Ascites grade	54 (15.5)	53 (21.3)

Table 28. Hepatic History in the Integrated Phase 3 Studies (Safety Population)

Parameter	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Possible precipitating factors for HRS		
Infection	57 (16.3)	43 (17.3)
GI bleeding	19 (5.4)	16 (6.4)
Large volume paracentesis	44 (12.6)	34 (13.7)
Diuretic treatment	47 (13.5)	35 (14.1)
Other	18 (5.2)	24 (9.6)
None of the above events/conditions	178 (51.0)	103 (41.4)

GI, gastrointestinal; HRS, hepatorenal syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group.

7.2.6 Subject Disposition

In the integrated analysis, 46.7% of subjects in the terlipressin group and 47.4% of subjects in the placebo group completed the study (CONFIRM and REVERSE) or returned for the 180-day visit (Section 5.3.1; Table 29). The most common reason for study discontinuation in both treatment groups was AE/death (terlipressin 49.0%, placebo 48.6%).

Table 29. Subject Disposition Overview in the Integrated Phase 3 Studies (Safety Population)

	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	**Placebo N=249 n (%)**
Randomized	349 (100)	249 (100)
Treated	349 (100)	249 (100)
End of study[a]		
Completed last follow-up visit	163 (46.7)	118 (47.4)
Discontinued due to		
AE/death[b,c]	171 (49.0)	121 (48.6)
Subject withdrew/withdrew informed consent	6 (1.7)	3 (1.2)
Subject lost to follow-up	1 (0.3)	1 (0.4)
Other	8 (2.3)	6 (2.4)

AE, adverse event; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group.

a. For CONFIRM and REVERSE, data represent status at the completion of their respective studies. For Study OT-0401, data represent those who returned for the 180-day follow-up visit.

b. In REVERSE, 28 subjects who ended the study due to death were recorded as other but are counted as AE/death in this table.

c. In OT-0401, 61 subjects died before completion of the end of study visit and are counted as AE/Death.

The most common reasons for discontinuation (Table 30) of study treatment for terlipressin-treated subjects in the integrated studies were meeting the primary endpoint and lack of efficacy. For placebo-treated subjects in the integrated studies, the most common reason for discontinuation was lack of efficacy.

Table 30. Reasons for Study Treatment Discontinuation in the Integrated Phase 3 Studies (Safety Population)

Reason	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Met primary endpoint[a]	103 (29.5)	37 (14.9)
Received maximum duration of study treatment per protocol/received 14 days of study treatment	26 (7.4)	18 (7.2)
Lack of efficacy[b]	103 (29.5)	101 (40.6)
Transplant	26 (7.4)	17 (6.8)
Death	4 (1.1)	1 (0.4)
Request of subject or legal authorized representative	9 (2.6)	10 (4.0)
Hospice/comfort/palliative care	8 (2.3)	3 (1.2)
AE	40 (11.5)	12 (4.8)
Transjugular intrahepatic portosystemic shunt	1 (0.3)	0
Protocol violation	0	0
Withdrew consent/withdrawal of consent for study participation, including follow-up	5 (1.4)	4 (1.6)
Physician decision/administrative decision	15 (4.3)	28 (11.2)
Other	17 (4.9)	21 (8.4)

AE, adverse event; HRS, hepatorenal syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SCr, serum creatinine.

a. This includes Verified HRS Reversal, Confirmed HRS Reversal, and treatment success.

b. This includes treatment failure, renal replacement therapy, and SCr at or above baseline value.

7.2.7 Adverse Events

7.2.7.1 Overview of Adverse Events

In the integrated studies, there were high incidences of AEs, SAEs, and mortality in both treatment groups. The incidences of all AEs and deaths up to 30 days after the EOT and 90 days from the start of treatment were generally similar between the treatment groups (Table 31). A greater percentage of terlipressin-treated subjects withdrew from the study treatment because of an AE compared with placebo-treated subjects. Of the 13.5% of patients who discontinued in the terlipressin group, 4.6% were for gastrointestinal events, 3.7% were for ischemic events, 3.4% were for respiratory-related events, and 1.8% were for other events.

Table 31. AE Profile in the Integrated Phase 3 Studies (Safety Population)

Safety Parameter[a]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
AEs up to 7 days post-treatment		
All	318 (91.1)	225 (90.4)
Related[b]	147 (42.1)	60 (24.1)
SAEs up to 30 days post-treatment		
All	227 (65.0)	149 (59.8)
Related[b]	24 (6.9)	5 (2.0)
Deaths up to 30 days post-treatment[c]		
All	145 (41.5)	101 (40.6)
Related[b]	4 (1.1)	0
AEs leading to death up to 90 days from the start of study treatment[d]	169 (48.4)	115 (46.2)
Dose interruptions due to AEs		
All	27 (7.7)	8 (3.2)
Related	20 (5.7)	3 (1.2)
Permanent withdrawals due to AEs		
All	47 (13.5)	13 (5.2)
Related[b]	29 (8.3)	7 (2.8)

AE, adverse event; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.

a. Subjects experiencing multiple episodes of a given adverse event were counted once per category.

b. Considered by the study investigators to be possibly or probably causally related to study treatment.

c. Up to 30 days post-treatment ranges from start of treatment on Day 1 to Day 46, corresponding to a maximum of 16 days of treatment for REVERSE plus 30 days.

d. For REVERSE, AE information for deaths was recorded through 90 days from the start of study drug in the Argus safety database.

Note: Initial and retreatment periods were combined.

7.2.7.2 Common AEs

In the integrated studies, the overall percentage of subjects with AEs was similar between the treatment groups (Table 32). The high number of AEs in both groups reflects the underlying advanced liver disease in the study population.

Table 32. AEs in ≥5% of Subjects in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Any AE	318 (91.1)	225 (90.4)
Abdominal pain	75 (21.5)	31 (12.4)
Nausea	53 (15.2)	30 (12.0)
Diarrhea	52 (14.9)	14 (5.6)
Dyspnea	42 (12.0)	15 (6.0)
Hypotension	41 (11.7)	19 (7.6)
Vomiting	36 (10.3)	16 (6.4)
Hypokalemia	32 (9.2)	20 (8.0)
Hepatic encephalopathy	30 (8.6)	28 (11.2)
Pulmonary edema	29 (8.3)	14 (5.6)
Respiratory failure	29 (8.3)	9 (3.6)
Anemia	28 (8.0)	21 (8.4)
Fluid overload	28 (8.0)	9 (3.6)
Bradycardia	22 (6.3)	2 (0.8)
Metabolic acidosis	22 (6.3)	15 (6.0)
Multiple organ dysfunction syndrome	19 (5.4)	8 (3.2)
Pain in extremity	19 (5.4)	2 (0.8)
Pleural effusion	19 (5.4)	5 (2.0)
Pneumonia	18 (5.2)	8 (3.2)

AE, adverse event; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group.
a. Up to 7 days after the end of treatment.
b. Subjects experiencing multiple episodes of a given AE were counted once with each preferred term.
Note: Initial and retreatment periods were combined.

7.2.7.3 Deaths

Deaths during the study occurred in a similar percentage for terlipressin- and placebo-treated subjects at all time points in the integrated phase 3 studies (Table 33) and in OT-0401 and REVERSE (Table 34). Approximately half of all reported deaths in both integrated groups occurred by Day 14, consistent with advanced liver disease and renal failure in patients with HRS-1.

Table 33. Death by Timing in the Integrated Phase 3 Studies (Safety Population)

Timing of Death[a]	Terlipressin N=349 n (%)	Placebo N=249 n (%)
During study treatment	16 (4.6)	11 (4.4)
By Day 7	41 (11.7)	32 (12.9)
By Day 14	87 (24.9)	60 (24.1)
By Day 30	133 (38.1)	88 (35.3)
By Day 60	157 (45.0)	111 (44.6)
By Day 90	168 (48.1)	120 (48.2)
Any time during the study[a]	170 (48.7)	120 (48.2)

N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group.

a: Included deaths prior to 90 days and deaths where the date of death was unknown. If the exact date of death was unknown, the subject was not included in the specific date rows in the table but is included in the "Any time during the study" group . Start of treatment is Day 1.

Death timing is determined using date of death. Two deaths were reported in CONFIRM without a date of death; hence they were captured under death at "Any time during the study". Subject (b) (6) 's final contact date was Day 91; Subject (b) (6) 's final contact date was Day 79; the site became aware of the subjects' deaths at these contacts.

Table 34. Death by Timing in the CONFIRM, REVERSE, and OT-0401 Studies (Safety Population)

	CONFIRM		REVERSE		OT-401	
Timing of Death[a]	**Terlipressin N=349 n (%)**	**Placebo N=249 n (%)**	**Terlipressin N=93 n (%)**	**Placebo N=95 n (%)**	**Terlipressin N=56 n (%)**	**Placebo N=5 n (%)**
During study treatment	9 (4.5)	1 (1.0)	0	3 (3.2)	7 (12.5)	7 (12.7)
By Day 7	22 (11.0)	11 (11.1)	6 (6.5)	10 (10.5)	13 (23.2)	11 (20.0)
By Day 14	53 (26.5)	24 (24.2)	18 (19.4)	19 (20.0)	16 (28.6)	17 (30.9)
By Day 30	78 (39.0)	36 (36.4)	30 (32.3)	31 (32.6)	25 (44.6)	21 (38.2)
By Day 60	94 (47.0)	41 (41.4)	34 (36.6)	40 (42.1)	29 (51.8)	30 (54.5)
By Day 90	100 (50.0)	44 (44.4)	39 (41.9)	43 (45.3)	29 (51.8)	33 (60.0)
Any time during the study[a]	102 (51.0)	44 (44.4)	39 (41.9)	43 (45.3)	29 (51.8)	33 (60.0)

N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group.

a: Included deaths prior to 90 days and deaths where the date of death was unknown. If the exact date of death was unknown, the subject was not included in the specific date rows in the table but is included in the "Any time during the study" group . Start of treatment is Day 1.

Death timing is determined using date of death. Two deaths were reported in CONFIRM without a date of death; hence they were captured under death at "Any time during the study". Subject (b) (6) 's final contact date was Day 91; Subject (b) (6) 's final contact date was Day 79; the site became aware of the subjects' deaths at these contacts.

As expected in a population with decompensated cirrhosis, mortality rates were high and AEs in the Hepatobiliary Disorders SOC were the most common fatal events up to 30 days post-treatment (terlipressin 18.9%, placebo 22.9%) and 90 days from the start of treatment (terlipressin 22.3%, placebo 24.9%). The most commonly reported AEs (≥5%) leading to death within 30 days post-treatment were MODS, chronic hepatic failure, and hepatic failure in the terlipressin integrated group and hepatic failure and chronic hepatic failure in the placebo integrated group (Table 35). Within 90 days from the start of treatment, the most commonly reported AEs leading to death were chronic hepatic failure, MODS, hepatic failure, and respiratory failure in the terlipressin integrated group and hepatic failure and chronic hepatic failure in the placebo integrated group (Table 36). MODS, respiratory failure, and sepsis were reported more frequently for terlipressin-treated subjects (≥2% difference between treatment groups) as AEs leading to death by 30 days post-treatment and 90 days after the start of treatment, while hepatic failure and HRS were reported more frequently for placebo-treated subjects. At 90 days, death from septic shock was also more frequently reported for terlipressin-treated subjects compared with placebo-treated subjects.

Table 35. AEs Leading to Death up to 30 Days Post-Treatment by Preferred Term in ≥2 Subjects in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
AEs leading to death	145 (41.5)	101 (40.6)
MODS	22 (6.3)	8 (3.2)
Chronic hepatic failure	21 (6.0)	15 (6.0)
Hepatic failure	20 (5.7)	22 (8.8)
Respiratory failure	17 (4.9)	3 (1.2)
Sepsis	11 (3.2)	3 (1.2)
Acute respiratory failure	8 (2.3)	2 (0.8)
Septic shock	8 (2.3)	1 (0.4)
HRS	7 (2.0)	11 (4.4)
Hepatic cirrhosis	6 (1.7)	2 (0.8)
Renal failure	6 (1.7)	3 (1.2)
Cirrhosis alcoholic	5 (1.4)	4 (1.6)
Shock	4 (1.1)	2 (0.8)
Hepatic encephalopathy	3 (0.9)	2 (0.8)
Esophageal varices hemorrhage	3 (0.9)	1 (0.4)
Pneumonia aspiration	3 (0.9)	0
Acute respiratory distress syndrome	2 (0.6)	1 (0.4)
Cardiorespiratory arrest	2 (0.6)	0
Hepatitis alcoholic	2 (0.6)	1 (0.4)
Hepatorenal failure	2 (0.6)	1 (0.4)
Pulmonary edema	2 (0.6)	0
Renal impairment	2 (0.6)	0

AE, adverse event; HRS, hepatorenal syndrome; MODS, multiple organ dysfunction syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SOC, System Organ Class.

a: Up to 30 days post-treatment.

b: Subjects experiencing multiple episodes of a given AE are counted once within each preferred term and within each SOC. Death may be attributed to more than one preferred term for a subject.

Note: Initial and retreatment periods were combined.

Table 36. AEs Leading to Death up to 90 Days From the Start of Treatment by Preferred Term in ≥2 Subjects in the Integrated Terlipressin Group in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
AEs leading to death	169 (48.4)	115 (46.2)
Chronic hepatic failure	26 (7.4)	18 (7.2)
MODS	25 (7.2)	11 (4.4)
Hepatic failure	24 (6.9)	23 (9.2)
Respiratory failure	19 (5.4)	3 (1.2)
Sepsis	13 (3.7)	3 (1.2)
Septic shock	11 (3.2)	1 (0.4)
Acute respiratory failure	8 (2.3)	2 (0.8)
Hepatic cirrhosis	8 (2.3)	3 (1.2)
HRS	7 (2.0)	11 (4.4)
Cirrhosis alcoholic	6 (1.7)	4 (1.6)
Renal failure	6 (1.7)	4 (1.6)
Shock	4 (1.1)	2 (0.8)
Acute respiratory distress syndrome	3 (0.9)	1 (0.4)
Hepatic encephalopathy	3 (0.9)	2 (0.8)
Esophageal varices hemorrhage	3 (0.9)	1 (0.4)
Pneumonia aspiration	3 (0.9)	0
Acidosis	2 (0.6)	0
Cardiorespiratory arrest	2 (0.6)	0
Hepatitis alcoholic	2 (0.6)	1 (0.4)
Hepatorenal failure	2 (0.6)	1 (0.4)
Mental status changes	2 (0.6)	0
Pulmonary edema	2 (0.6)	0
Renal impairment	2 (0.6)	0
Upper GI hemorrhage	2 (0.6)	0

AE, adverse event; GI, gastrointestinal HRS, hepatorenal syndrome; MODS, multiple organ dysfunction syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SOC, System Organ Class.

a: Up to 90 days from the start of treatment.

b: Subjects experiencing multiple episodes of a given AE are counted once within each preferred term and within each SOC. Death may be attributed to more than one preferred term for a subject.

c: For REVERSE, AE information for deaths was recorded through 90 days from the start of study drug in the Argus safety database.

Note: Initial and retreatment periods were combined.

7.2.7.4 Serious Adverse Events

In the integrated studies, the types of SAEs were similar between treatment groups (Table 37). The overall incidence of SAEs was higher in the terlipressin group than in the placebo group.

The most frequently reported SAEs were respiratory failure, MODS, and chronic hepatic failure in the terlipressin group and hepatic failure, chronic hepatic failure, and HRS in the placebo group (Table 37). SAEs of respiratory failure, MODS, sepsis, abdominal pain, and GI hemorrhage were reported more frequently (≥2% difference between treatment groups) by terlipressin-treated subjects, while hepatic failure was reported more frequently by placebo-treated subjects. Respiratory failure was the only SAE reported ≥5% more frequently in the terlipressin group.

Table 37. SAEs in ≥2 of Subjects in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Any SAE	227 (65.0)	149 (59.8)
Respiratory failure	29 (8.3)	6 (2.4)
MODS	26 (7.4)	8 (3.2)
Chronic hepatic failure	21 (6.0)	15 (6.0)
Hepatic failure	21 (6.0)	23 (9.2)
Sepsis	18 (5.2)	4 (1.6)
Abdominal pain	15 (4.3)	2 (0.8)
Acute respiratory failure	11 (3.2)	5 (2.0)
HRS	11 (3.2)	12 (4.8)
GI hemorrhage	10 (2.9)	1 (0.4)
Hepatic encephalopathy	10 (2.9)	9 (3.6)
Renal failure	10 (2.9)	6 (2.4)
Pneumonia	9 (2.6)	8 (3.2)
Septic shock	9 (2.6)	2 (0.8)
Acute kidney injury	8 (2.3)	5 (2.0)
Esophageal varices hemorrhage	7 (2.0)	4 (1.6)

Table 37. SAEs in ≥2 of Subjects in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Pulmonary edema	7 (2.0)	3 (1.2)
Hypotension	7 (2.0)	4 (1.6)

GI, gastrointestinal; HRS, hepatorenal syndrome; MODS, multiple organ dysfunction syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.

a: Up to 30 days post-treatment.

b: Subjects experiencing multiple AEs are counted once within the preferred term.

Note: Initial and retreatment periods were combined.

7.2.7.5 Adverse Events of Special Interest (AESI)

Three categories of AESIs were included in the CONFIRM and REVERSE protocols to evaluate their potential relationship to intestinal ischemia, serious cardiac events, and more significant respiratory events. These AESIs were chest pain, abdominal pain, and dyspnea/wheezing/ bronchospasm/pulmonary edema.

7.2.7.5.1 Chest Pain

In CONFIRM and REVERSE, the AESI of chest pain was reported at a low frequency (Table 38). Chest pain was not captured as an AESI in OT-0401; however, the occurrence of the AE of chest pain was also low for terlipressin-treated subjects (0%) and placebo-treated subjects (3.6%) in this study.

The majority of AESIs of chest pain were considered mild or moderate and all were resolved or resolved with sequalae (Table 36). Three subjects in the terlipressin group had their dose of study drug decreased because of the event and 1 subject in each treatment group had the study drug permanently discontinued because of the event.

An ECG was used to evaluate the majority of these AESIs; 1 subject in the terlipressin group and 2 subjects in the placebo group had significantly abnormal ECG results. Myocardial ischemia testing, chest x-ray, and “other” tests were also performed to evaluate these AESIs.

Table 38. Chest Pain AESIs in the Integrated REVERSE and CONFIRM Studies

Chest Pain AESI[a]	Integrated REVERSE + CONFIRM			
	Terlipressin N=293		Placebo N=194	
	Subjects n (%)[b]	Events n	n (%)[b]	Events n
Overall	16 (5.5)	17	8 (4.1)	8
Severity[c]				
Mild	5 (1.7)	5	5 (2.6)	5
Moderate	10 (3.4)	11	3 (1.5)	3
Severe	1 (0.3)	1	0	0
Resolved or resolved with sequelae	16 (5.5)	17	8 (4.1)	8
Action taken[c]				
Dose increased	0	0	0	0
Dose decreased	3 (1.0)	3	0	0
Dose stopped temporarily	0	0	0	0
Drug permanently stopped	1 (0.3)	1	1 (0.5)	1

AE, adverse event; AESI, adverse event of special interest; N, number of subjects in the treatment group; n for subjects, number of subjects in the category of subjects in the treatment group; n for events, number of events in the category of subjects in the treatment group.
a: Up to 7 days post-treatment for AEs and up to 30 days post-treatment for SAEs.
b: Subjects experiencing multiple AEs are counted once.
c: Subjects are counted within the most severe category for severity and within the worst action taken category (dose permanently stopped, temporarily stopped, decreased, increased).

7.2.7.5.2 Abdominal Pain

In CONFIRM and REVERSE, a higher percentage of subjects in the terlipressin group had a moderate or severe AESI of abdominal pain compared with subjects in the placebo group, and the majority of subjects had events that were considered resolved or resolved with sequalae (Table 39). Ten subjects in the terlipressin group and 1 subject in the placebo group permanently discontinued study drug because of the AESI. Abdominal pain was not captured as an AESI in OT-0401; however, the occurrence of the AE of abdominal pain was 10.7% in the terlipressin group and 7.3% in the placebo group in this study.

Table 39. Abdominal Pain AESIs in the Integrated REVERSE and CONFIRM Studies

	Integrated REVERSE + CONFIRM			
	Terlipressin N=293		Placebo N=194	
Abdominal Pain AESI[a]	Subjects n (%)[b]	Events n	n (%)[b]	Events n
Overall	89 (30.4)	112	34 (17.5)	36
Severity[c]				
Mild	28 (9.6)	37	19 (9.8)	21
Moderate	41 (14.0)	51	15 (7.7)	15
Severe	20 (6.8)	24	0	0
Resolved or resolved with sequelae	73 (24.9)	92	28 (14.4)	30
Action taken[c]				
Dose increased	0	0	0	0
Dose decreased	6 (2.0)	6	1 (0.5)	1
Dose stopped temporarily	5 (1.7)	5	1 (0.5)	1
Drug permanently stopped	10 (3.4)	11[d]	1 (0.5)	1

AE, adverse event; AESI, adverse event of special interest; N, number of subjects in the treatment group; n for subjects, number of subjects in the category of subjects in the treatment group; n for events, number of events in the category of subjects in the treatment group.
a: Up to 7 days post-treatment for AEs and up to 30 days post-treatment for SAEs.
b: Subjects experiencing multiple AEs are counted once.
c: Subjects are counted within the most severe category for severity and within the worst action taken category (dose permanently stopped, temporarily stopped, decreased, increased).
d. Two AEs were recorded for 1 patient.

7.2.7.5.3 Dyspnea, Wheezing, Bronchospasm, and/or Pulmonary Edema

In CONFIRM and REVERSE, 102 terlipressin-treated subjects (34.8%) and 38 placebo-treated subjects (19.6%) reported AESIs of dyspnea, wheezing, bronchospasm, and/or pulmonary edema (Table 40). A higher percentage of subjects in the terlipressin group had a moderate or severe AESI of dyspnea, wheezing, bronchospasm and/or pulmonary edema compared with subjects in the placebo group. The majority of subjects had events that resolved or resolved with sequalae. Nine subjects in the terlipressin group and 1 subject in the placebo group permanently discontinued the study drug because of the AESI.

Table 40. Dyspnea, Wheezing, Bronchospasm, and Pulmonary Edema AESIs in the Integrated REVERSE and CONFIRM Studies

Dyspnea, Wheezing, Bronchospasm, and Pulmonary Edema AESI[a]	Integrated REVERSE + CONFIRM			
	Terlipressin N=293		Placebo N=194	
	Subjects n (%)[b]	Events n	n (%)[b]	Events n
Overall	102 (34.8)	140	38 (19.6)	53
Severity[c]				
Mild	26 (8.9)	37	11 (5.7)	18
Moderate	41 (14.0)	61	16 (8.2)	23
Severe	35 (11.9)	42	11 (5.7)	12
Resolved or resolved with sequelae	65 (22.2)	87	25 (12.9)	31
Action taken[c]				
Dose increased	0	0	0	0
Dose decreased	2 (0.7)	2	0	0
Dose stopped temporarily	5 (1.7)	6	0	0
Drug permanently stopped	9 (3.1)	9	1 (0.5)	1

AE, adverse event; AESI, adverse events of special interest; N, number of subjects in the treatment group; n for subjects, number of subjects in the category of subjects in the treatment group; n for events, number of events in the category of subjects in the treatment group.
a: Up to 7 days post-treatment for AEs and up to 30 days post-treatment for SAEs.
b: Subjects experiencing multiple adverse events are counted once.
c: Subjects are counted within the most severe category for severity and within the worst action taken category (dose permanently stopped, temporarily stopped, decreased, increased).

7.2.7.6 Adverse Events Leading to Withdrawal

In the integrated studies, 47 subjects (13.5%) in the terlipressin group had AEs that led to permanent withdrawal from study treatment compared with 13 subjects (5.2%) in the placebo group (Table 41), an incidence in the terlipressin group that is consistent with reports in the literature (approximately 13%; Facciorusso 2017, Gluud 2012).

Table 41. AEs Leading to Withdrawal by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Overall	47 (13.5)	13 (5.2)
Abdominal pain	6 (1.7)	0
Intestinal ischemia	4 (1.1)	0
Respiratory failure	4 (1.1)	1 (0.4)
Acute respiratory failure	3 (0.9)	0
Cyanosis	3 (0.9)	0
GI hemorrhage	3 (0.9)	1 (0.4)
Pulmonary edema	3 (0.9)	1 (0.4)
Atrial fibrillation	2 (0.6)	1 (0.4)
Diarrhea	2 (0.6)	0
Hypotension	2 (0.6)	3 (1.2)
Hypoxia	2 (0.6)	0
Pain in extremity	2 (0.6)	0
Shock	2 (0.6)	0
Vascular skin disorder	2 (0.6)	0
Vomiting	2 (0.6)	0
Abdominal pain upper	1 (0.3)	0
Blood creatinine increased	1 (0.3)	0
Chest pain	1 (0.3)	1 (0.4)
Chronic hepatic failure	1 (0.3)	0
Circulatory collapse	1 (0.3)	0
Disseminated intravascular coagulation	1 (0.3)	0
Dyspnea	1 (0.3)	0
Electrocardiogram change	1 (0.3)	0
Hematoma	1 (0.3)	0
Hypertension	1 (0.3)	0
Intestinal obstruction	1 (0.3)	0
Livedo reticularis	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Nausea	1 (0.3)	1 (0.4)
Esophageal varices hemorrhage	1 (0.3)	0
Pancytopenia	1 (0.3)	0
Poor peripheral circulation	1 (0.3)	0
Pulseless electrical activity	1 (0.3)	0
Respiratory tract infection	1 (0.3)	0
Skin discoloration	1 (0.3)	0
Tachypnoea	1 (0.3)	0

Preferred Term[a,b]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Testicular infarction[c]	1 (0.3)	0
Acute kidney injury	0	1 (0.4)
Arrhythmia	0	1 (0.4)
Ascites	0	1 (0.4)
Azotemia	0	1 (0.4)
Chills	0	1 (0.4)
Ileus	0	1 (0.4)
Myocardial ischemia	0	1 (0.4)
Tachycardia	0	2 (0.8)
Ventricular tachycardia	0	1 (0.4)

AE, adverse event; GI, gastrointestinal; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SOC; system organ class.
a. Up to 7 days post-treatment. For REVERSE and CONFIRM, only AEs where action taken was reported as permanently stopped were included. For OT-0401, permanent withdrawals due to an AE occurred when action taken was reported as permanently stopped or discontinued permanently.
b. Subjects experiencing multiple AEs are counted once within the preferred term.
c. Subject (b) (6) had an event of scrotal tissue infarction (verbatim term) which was incorrectly coded as testicular infarction. The event was incorrectly coded to the Reproductive System and Breast Disorders SOC and subsequently recoded to be included in the Skin and Subcutaneous Tissue Disorder SOC as subcutaneous tissue infarction.
Note: Initial and retreatment periods were combined.

Among the 47 subjects who discontinued terlipressin treatment, 13 subjects were considered to have experienced ischemic AEs (See Section 7.2.7.8.5 for further details about the evaluation of ischemic events). Unlike in OT-0401, treatment was permanently discontinued in CONFIRM and REVERSE if a disqualifying ischemic event was suspected. In CONFIRM and OT-0401, permanent withdrawal only occurred with cardiac ischemia or mesenteric ischemia cases; subjects were allowed to resume study drug if a peripheral ischemic event had resolved. In REVERSE, study drug was discontinued for any central or peripheral ischemic events.

7.2.7.7 Adverse Events Leading to Dose Interruptions

In the integrated studies, 27 subjects (7.7%) in the terlipressin group had AEs that led to dose interruptions compared with 8 subjects (3.2%) in the placebo group. Of these, 20 subjects (5.7%) in the terlipressin group and 3 subjects (1.2%) in the placebo group had AEs leading to dose interruption that were considered by the investigator to be related to study drug. The most common AE leading to dose interruption for both treatment groups was abdominal pain. All other AEs leading to dose interruptions were reported by ≤2 subjects per treatment group.

7.2.7.8 Analysis of Adverse Events by Organ System or Syndrome

Based on the mechanism of action of terlipressin or the frequency at which certain AEs occurred in the clinical studies, further evaluations based on specific organ systems or syndromes were performed for the categories associated with Cardiac Disorders, GI Disorders, infection, ischemia, MODS, and Respiratory Disorders.

7.2.7.8.1 Cardiac Disorders

In the integrated studies, 74 terlipressin-treated subjects (21.2%) and 37 placebo-treated subjects (14.9%) reported AEs in the Cardiac Disorders SOC. The most frequently reported cardiac-associated AEs in the terlipressin group were bradycardia, atrial fibrillation, and tachycardia.

A pre-existing cardiac disorder was reported for 120 terlipressin-treated subjects (34.4%) and 83 placebo-treated subjects (33.3%). The incidence of prior use of cardiac medications was similar between the treatment groups (terlipressin 84.5%, placebo 85.5%). Use of cardiac medications generally decreased on-study for both terlipressin-treated and placebo-treated subjects. Diuretics were used by a higher percentage of subjects in the integrated terlipressin group (26.9%) compared with the placebo group (17.7%).

Adverse events in the Cardiac Disorders SOC leading to withdrawal were reported for 7 terlipressin-treated subjects (2.0%), including atrial fibrillation (n=2), cyanosis (n=3), myocardial infarction, and pulseless electrical activity (n=1 each) and 5 placebo-treated subjects (2.0%), including tachycardia (n=2), arrhythmia, atrial fibrillation, myocardial ischemia, and ventricular tachycardia (n=1 each).

In the integrated studies, 20 terlipressin-treated subjects (5.7%) and 20 placebo-treated subjects (8.0%) experienced SAEs in the Cardiac Disorders SOC (Table 42). The most frequently identified SAEs were cardiac arrest, atrial fibrillation, and cardiorespiratory arrest.

Cardiac SAEs that were considered related to the study drug were reported for 4 terlipressin-treated subjects (1.1%; [atrial fibrillation, cyanosis, myocardial infarction, and supraventricular tachycardia]) and 4 placebo-treated subjects (1.6%; arrhythmia [n=2], atrial fibrillation [n=2], and myocardial ischemia [n=1]). Two terlipressin-treated subjects (0.6%) had an AE in the Cardiac Disorders SOC associated with a fatal outcome within 30 days from the start of treatment, compared with 6 subjects (2.4%) in the placebo group. Two terlipressin-treated subjects (0.6%) had a cardiac AE associated with fatal outcome within 90 days from the start of treatment, compared with 7 subjects (2.8%) in the placebo group.

Table 42. Cardiac Disorder Deaths and SAEs in >1 Subject in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Cardiac Disorder SAEs	20 (5.7)	20 (8.0)
Atrial fibrillation	3 (0.9)	4 (1.6)
Cardiac arrest	4 (1.1)	4 (1.6)
Cardiorespiratory arrest	3 (0.9)	1 (0.4)
Pulseless electrical activity	2 (0.6)	1 (0.4)
Deaths[b] from Cardiac Disorders	2 (0.6)	7 (2.8)
Cardiorespiratory arrest	2 (0.6)	0

AE, adverse event; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.

a. Subjects experiencing multiple AEs are counted once within the preferred term.

b. Up to 90 days following the start of treatment.

Note: Initial and retreatment periods were combined.

7.2.7.8.1.1 Bradycardia

Bradycardia is an expected event for terlipressin based on its pharmacological mechanism of action, resulting in increased MAP triggering a baroflex-induced decreased heart rate. As expected, the incidence of bradycardia was higher in the terlipressin-treated integrated group (n=22 [6.3%]) compared with the placebo-treated integrated group (n=2 [0.8%]). None of the events of bradycardia was serious; 18 of 25 bradycardia events in the terlipressin group and the 2 events in the placebo group were considered severe. The majority of subjects with bradycardia events did not require a change in dose (terlipressin 72.7%, placebo 50.0%), and the majority of subjects with these events recovered or resolved without sequalae (terlipressin 86.4%, placebo 50.0%).

Most events of bradycardia occurred during treatment. The recorded outcome of most events of bradycardia was recovered/resolved or recovered with sequelae, with only 1 not recovered/not resolved event and 1 recovering/resolving event. One subject experienced 2 episodes of bradycardia, 1 on Day 1 (recovered), another on Day 6. Approximately half of the events of bradycardia in the terlipressin group were considered to be related to the study drug. Both events in the placebo group were considered unrelated to study drug. No action was taken for most events, with dose being decreased for 2 events and study drug being interrupted for 1 event.

7.2.7.8.1.2 Arrhythmias

The incidence of AEs related to arrhythmia was low and similar for the integrated terlipressin and placebo groups. The incidence of atrial fibrillation and ventricular tachycardia was 13 subjects (3.7%) and 4 subjects (1.1%) for the terlipressin group and 11 subjects (4.4%) and 3 subjects (1.2%) for the placebo group, respectively. All other arrhythmia AEs occurred in <1% of either treatment group.

7.2.7.8.2 Gastrointestinal Disorders

Gastroparesis, a significant decrease in gastric emptying without the presence of mechanical obstruction, is common in cirrhotic patients, as are other GI symptoms. Existing parasympathetic impairment and increased sympathetic drive of the autonomic system may be responsible for vasopressin-induced gastric dysrhythmia and its clinical consequences (Furgala 2011). Gastrointestinal AEs, including abdominal pain, vomiting, and diarrhea, have been commonly reported with terlipressin use; most GI AEs appear to be mild and transient (Krag 2011). Nonocclusive mesenteric ischemia is the result of splanchnic vasoconstriction occurring in response to a variety of systemic insults that diminishes mesenteric blood flow; these insults include decreased cardiac output (pump failure or arrhythmias), hypovolemia, hypotension (due to shock or sepsis), rapid digitalization, or reaction to vasopressors (Kim 2013).

In the integrated studies, more terlipressin-treated subjects had GI AEs (52.1%) than did placebo-treated subjects (42.6%). Differences of ≥2% between the terlipressin and placebo treatment groups in the incidence of individual GI AEs were observed for abdominal pain (21.5% vs 12.4%), nausea (15.2% vs 12.0%), diarrhea (14.9% vs 5.6%), vomiting (10.3% vs 6.4%), and abdominal distension (4.0% vs 2.0%), all of which were higher in terlipressin-treated subjects.

The most frequent SAEs reported in >2 subjects in either treatment group in the GI Disorders SOC included abdominal pain, GI hemorrhage, esophageal varices hemorrhage, ascites, intestinal ischemia, upper GI hemorrhage, and vomiting (Table 43). Deaths related to AEs in the GI disorders SOC were reported for 5 terlipressin-treated subjects (1.4%) and 3 placebo-treated subjects (1.2%) within 30 days and 6 terlipressin-treated subjects (1.7%) and 3 placebo-treated subjects (1.2%) within 90 days from the start of study treatment.

Adverse events in the GI disorders SOC leading to withdrawal were reported for 16 terlipressin-treated subjects (4.6%) and for 3 placebo-treated subjects (1.2%). The GI AEs leading to withdrawal included abdominal pain (n=6 subjects), intestinal ischemia (n=4), GI hemorrhage (n=3), diarrhea (n=2), vomiting (n=2), and abdominal pain upper, intestinal obstruction, nausea, and esophageal varices hemorrhage (n=1 each) for the terlipressin integrated group (more than 1 AE could be reported for a subject's withdrawal) and ascites, GI hemorrhage, and ileus (n=1 subject each) for the placebo integrated group.

Table 43. Gastrointestinal Disorder Deaths and SAEs in >1 Subject in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Gastrointestinal Disorder SAEs	48 (13.8)	18 (7.2)
Abdominal pain	15 (4.3)	2 (0.8)
GI hemorrhage	10 (2.9)	1 (0.4)
Esophageal varices hemorrhage	7 (2.0)	4 (1.6)
Ascites	4 (1.1)	3 (1.2)
Intestinal ischemia	4 (1.1)	0
Upper GI hemorrhage	3 (0.9)	4 (1.6)
Vomiting	3 (0.9)	0
Lower GI hemorrhage	2 (0.6)	0
Nausea	2 (0.6)	0
Deaths[b] from Gastrointestinal Disorders	6 (1.7)	3 (1.2)
Esophageal varices hemorrhage	3 (0.9)	1 (0.4)
Upper GI hemorrhage	2 (0.6)	0

AE, adverse event; GI, gastrointestinal; ; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.
a. Subjects experiencing multiple AEs are counted once within the preferred term.
b. Up to 90 days following the start of treatment.
Note: Initial and retreatment periods were combined.

7.2.7.8.3 Fluid Overload

Patients with severely advanced decompensated cirrhosis are at an increased risk of developing cardiopulmonary complications, including fluid overload.

While terlipressin, by improving renal function, can ameliorate fluid overload, terlipressin cardiopulmonary effects can potentially unmask or exacerbate fluid overload in some patients, particularly in the setting of prior albumin use. There was a higher prior albumin use over the course of the 3 studies as a result in changes in the Practice Guidelines for the use of albumin in patients with decompensated cirrhosis and HRS-1 (CONFIRM > REVERSE > OT-0401) (Table 44). This likely accounts for the higher difference in incidence of fluid overload for terlipressin vs. placebo in CONFIRM (Table 45). The importance of this change in treatment guidelines regarding the use of albumin to treat HRS-1 is discussed in detail in Section 8.2.

Table 44. Prior Albumin Exposure in the Terlipressin Clinical Studies

	OT-0401		REVERSE		CONFIRM	
	Terlipressin N=56	Placebo N=56	Terlipressin N=93	Placebo N=99	Terlipressin N=199	Placebo N=101
Overall prior albumin exposure, %	64.3	80.0	100.0	100.0	99.0	99.0
Mean total prior albumin exposure, g	-	-	243.2	218.1	335.0	370.7)

Table 45. Fluid Overload in the Individual Studies (Safety Population)

	CONFIRM		REVERSE		OT-0401	
Preferred Term[a,b]	Terlipressin N=200	Placebo N=99	Terlipressin N=93	Placebo N=95	Terlipressin N=56	Placebo N=55
Fluid overload, n (%)	17 (8.5)	3 (3.0)	9 (9.7)	5 (5.3)	2 (3.6)	1 (1.8)

a. Up to 7 days after the end of treatment.
b. Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.

Fluid overload in patients with decompensated cirrhosis should be initially managed by decreasing the administration of albumin and other fluids and judicious use of diuretics. As expected, based on a higher incidence of fluid overload in the terlipressin group, use of diuretics was higher and concomitant use of albumin was lower in the terlipressin group vs placebo in CONFIRM.

Concomitant diuretic use in subjects with adverse events in the Standardised MedDRA Query (SMQ) for Fluid Overload was 51.0% in the terlipressin group and 37.5% in the placebo group.

Concomitant albumin use was lower in the terlipressin group than placebo group in subjects who developed fluid overload, reflecting albumin restrictions (204.2 g vs. 237.5 g respectively). The majority of events of fluid overload had an outcome of resolved/resolving or resolved with sequalae and none of the events of fluid overload led to a fatal outcome.

7.2.7.8.4 Respiratory Disorders

Respiratory disorders are commonly reported in patients with decompensated cirrhosis. Their etiology is multifactorial and includes coincident primary respiratory disorders (eg, chronic obstructive pulmonary disease [COPD], asthma), pulmonary edema related to congestive heart failure with CAD, ascites with hepatic hydrothorax, and, less commonly, portopulmonary hypertension and hepatopulmonary syndrome (Rodriguez-Roisin 2008). Based on its pharmacodynamic activity, terlipressin is known to have cardiovascular and pulmonary effects

that include increased MAP, decreased cardiac output, increased systemic vascular resistance, decreased cardiac ejection fraction, increased end diastolic volume, and increased pulmonary vascular resistance (Narahara 2009, Krag 2010, Narahara 2012, Kalambokis 2012).

Terlipressin is a V_1 receptor-mediated constrictor of smooth muscle and, while the presence of V_1 receptors in bronchial muscle has not been demonstrated, V_1 receptors are present in pulmonary vascular endothelium. An effect on the pulmonary vasculature could indirectly affect the bronchial smooth muscle and lead to wheezing or bronchospasm. In addition, the presence of cirrhotic cardiomyopathy with cardiac diastolic dysfunction is common in patients with decompensated cirrhosis, especially those with HRS (Wong 2012); this disorder may present as respiratory AEs.

Respiratory-related AEs in the Respiratory, Thoracic, and Mediastinal Disorders SOC were reported more frequently in the terlipressin group (n=149, 42.7%) than in the placebo group (n=71, 28.5%). Dyspnea, pulmonary edema, respiratory failure, pleural effusion, acute respiratory failure, and wheezing were reported ≥2% more frequently in terlipressin-treated than placebo subjects, while epistaxis was reported more frequently by placebo-treated subjects.

In the terlipressin integrated group, 12 terlipressin-treated subjects (3.4%) withdrew from study drug because of respiratory-related AEs, with AEs of acute respiratory failure (n=3, 0.9%), hypoxia (n=2, 0.6% each), pulmonary edema (n=3, 0.9%) respiratory failure (n=4, 1.1%), and tachypnea and dyspnea (n=1, 0.3% each]), compared with 2 placebo-treated subjects (0.8%) with pulmonary edema and respiratory failure (n=1, 0.4% each). A single subject can have more than 1 respiratory-related AE leading to withdrawal.

More terlipressin-treated subjects than placebo-treated subjects had severe respiratory-related AEs, and respiratory-related SAEs (Table 46). Overall, 11.4% of terlipressin-treated subjects had respiratory failure SAEs, which includes the preferred terms respiratory failure and acute respiratory failure, compared with 4.4% of placebo-treated subjects. One subject had both a respiratory failure and an acute respiratory failure SAE. More terlipressin-treated subjects had respiratory AEs associated with a fatal outcome within 30 days and 90 days compared with their placebo-treated counterparts.

Table 46. Respiratory AEs Reported by >1 Subject in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Respiratory, Thoracic, and Mediastinal Disorders severe AEs	59 (16.9)	24 (9.6)
Respiratory failure	27 (7.7)	7 (2.8)
Acute respiratory failure	13 (3.7)	3 (1.2)
Pulmonary edema	9 (2.6)	3 (1.2)
Acute respiratory distress syndrome	5 (1.4)	1 (0.4)
Dyspnea	3 (0.9)	1 (0.4)
Hypoxia	3 (0.9)	2 (0.8)
Pneumonia aspiration	3 (0.9)	0
Respiratory distress	3 (0.9)	4 (1.6)
Respiratory, Thoracic, and Mediastinal Disorders SAEs	57 (16.3)	26 (10.4)
Respiratory failure	29 (8.3)	6 (2.4)
Acute respiratory failure	11 (3.2)	5 (2.0)
Pulmonary edema	7 (2.0)	3 (1.2)
Pneumonia aspiration	5 (1.4)	1 (0.4)
Acute respiratory distress syndrome	4 (1.1)	2 (0.8)
Dyspnea	3 (0.9)	0
Respiratory distress	2 (0.6)	4 (1.6)
Deaths[b] from Respiratory, Thoracic, and Mediastinal Disorders	33 (9.5)	11 (4.4)
Respiratory failure	19 (5.4)	3 (1.2)
Acute respiratory failure	8 (2.3)	2 (0.8)
Acute respiratory distress syndrome	3 (0.9)	1 (0.4)
Pneumonia aspiration	3 (0.9)	0
Pulmonary edema	2 (0.6)	0

AE, adverse event; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.

a. Subjects experiencing multiple AEs are counted once with the preferred term.

b. Up to 90 days from the start of treatment.

Note: Initial and retreatment periods were combined.

The incidence of AEs of respiratory failure was higher in the terlipressin group than in the placebo group (8.3% vs 3.6%, respectively). The incidence of AEs of acute respiratory failure was also higher in the terlipressin group than the placebo group (4.0% vs 1.2%, respectively). Most of these events were SAEs (respiratory failure: terlipressin 8.3%, placebo 2.4%; acute respiratory failure: terlipressin 3.2%, placebo 2.0%). Respiratory failure led to the death of 19

subjects (5.4%) in the terlipressin group compared with 3 subjects (1.2%) in the placebo group. A total of 8 subjects (2.3%) in the terlipressin group died of acute respiratory failure compared with 2 subjects (0.8%) in the placebo group.

A similar percentage of subjects in the integrated terlipressin and placebo groups had prior use of respiratory medications (terlipressin 23.8%, placebo 23.3%), with use decreasing on-study in the placebo group and remaining the same in the terlipressin group (terlipressin 22.3%, placebo 14.5%). The most commonly used concomitant respiratory medication therapeutic subgroup involved drugs for obstructive airway disease (terlipressin 18.3%, placebo 8.4%); the higher rate in the terlipressin group is consistent with its higher rate of respiratory AEs (terlipressin 42.7%, placebo 28.5%). More than half of the subjects in both the terlipressin and placebo group (53.9% and 51.4%, respectively) had prior use of diuretics, and a higher percentage of terlipressin-treated subjects (26.9%) compared with placebo-treated patients (17.7%) used diuretics concomitantly (on study), suggestive of fluid overload.

In aggregate, based on the cumulative data available, including detailed review of individual subjects, an effect of terlipressin leading to respiratory-related AEs, including respiratory failure/acute respiratory failure, cannot be excluded. Subjects with more advanced disease (MELD score ≥37, baseline grade 3 hepatic encephalopathy, ACLF grade 3), a significant history of prior or treatment-emergent cardiorespiratory events (eg, dyspnea, wheezing, cardiomegaly, pneumonia/aspiration pneumonia, atelectasis) or recent upper GI hemorrhage appear more likely to develop respiratory failure/acute respiratory failure with terlipressin treatment. Terlipressin should be used with caution in these patients and the dose of terlipressin should not be increased in subjects with treatment-emergent cardiorespiratory events.

Section 8.2 provides a detailed discussion of the risk of respiratory failure in some patients treated with terlipressin, including identification of patients who may be a higher risk for such events and proposed actions for mitigating this identified risk.

Patients with increasing dyspnea, cough, orthopnea, or tachypnea should be carefully evaluated for evidence of pulmonary edema. In subjects with fluid overload, especially those with respiratory events (dyspnea, respiratory distress), careful assessment of the volume of concomitant albumin and other fluids being administered should be undertaken; temporary albumin dose reduction or discontinuation may be the most appropriate initial management. Judicious, short-term use of temporary diuretic therapy as per standard-of-care may be employed in some patients in whom a response to diuretic therapy is expected. If respiratory symptoms persist, further management should include dose reduction or temporary interruption of terlipressin dosing.

7.2.7.8.5 Infections

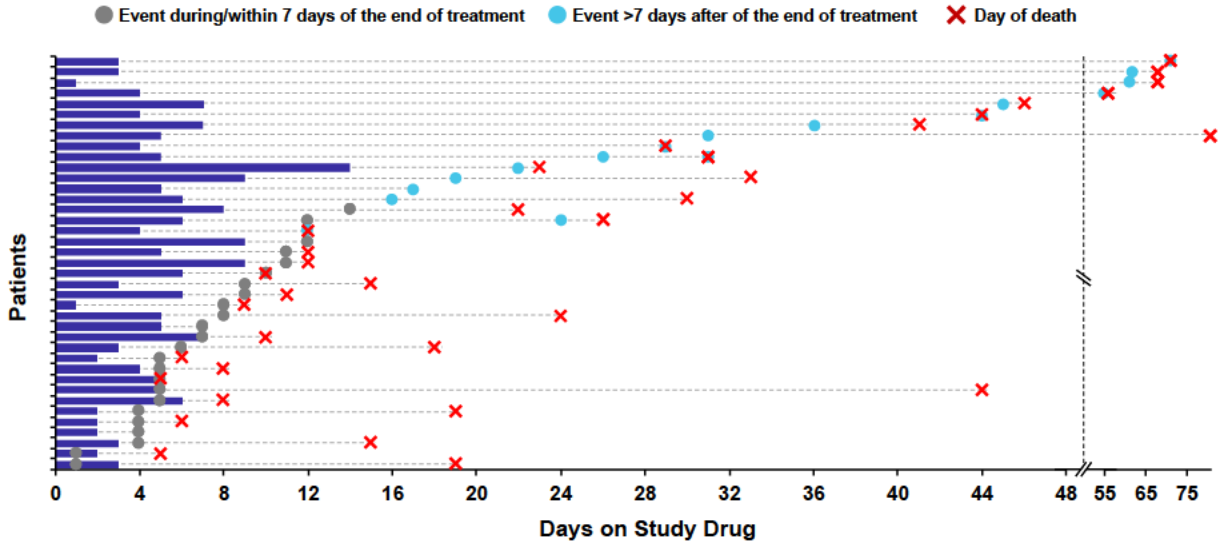
Bacterial infections are a common complication of cirrhosis. The rates of infection among hospitalized patients with cirrhosis range from 32% to 64% (Fernandez 2002, Borzio 2001, Merli

2010, Das 2010). Patients with decompensated cirrhosis and advanced ACLF are at high risk for infection and subsequent complications, including sepsis and septic shock (Tandon 2008). Sepsis is a common cause of death in patients with cirrhosis and decompensated cirrhosis, including those with HRS-1 (Cheruvattath 2007, Cholongitas 2006). Once infection develops, renal failure, shock, and encephalopathy may follow, adversely affecting survival. In-hospital mortality of cirrhotic subjects with infection is approximately 15%, more than twice that of cirrhotic subjects without infection. More importantly, infection is directly responsible for 30 to 50% of deaths in cirrhosis.

In the integrated studies, 91 terlipressin-treated subjects (26.1%) and 53 placebo-treated subjects (21.3%) experienced AEs coded to the infections and infestations SOC.

Combined sepsis AEs, which includes the preferred terms sepsis, septic shock, and urosepsis, were reported by 9.7% of subjects in the terlipressin group versus 4.0% in the placebo group through 30 days from the end of treatment. The majority of sepsis and septic shock events in the terlipressin group occurred after treatment, usually >72 hours, and frequently after >10 days (Figure 28).

Figure 28. Subjects With Sepsis AEs in the Integrated Phase 3 Terlipressin-Treatment Group (Safety Population)



AE, adverse event; N, number of subjects.
The blue bars indicate days on study drug and, for those who died, the red X's indicate date of death. The grey circles represent sepsis events that occurred during or within 7 days of the end of study drug treatment and the blue circles indicate sepsis events that occurred more than 7 days following the end of treatment. Sepsis AE includes abdominal sepsis, enterococcal sepsis, klebsiella sepsis, septic shock, sepsis syndrome, sepsis, and urosepsis. N=41.

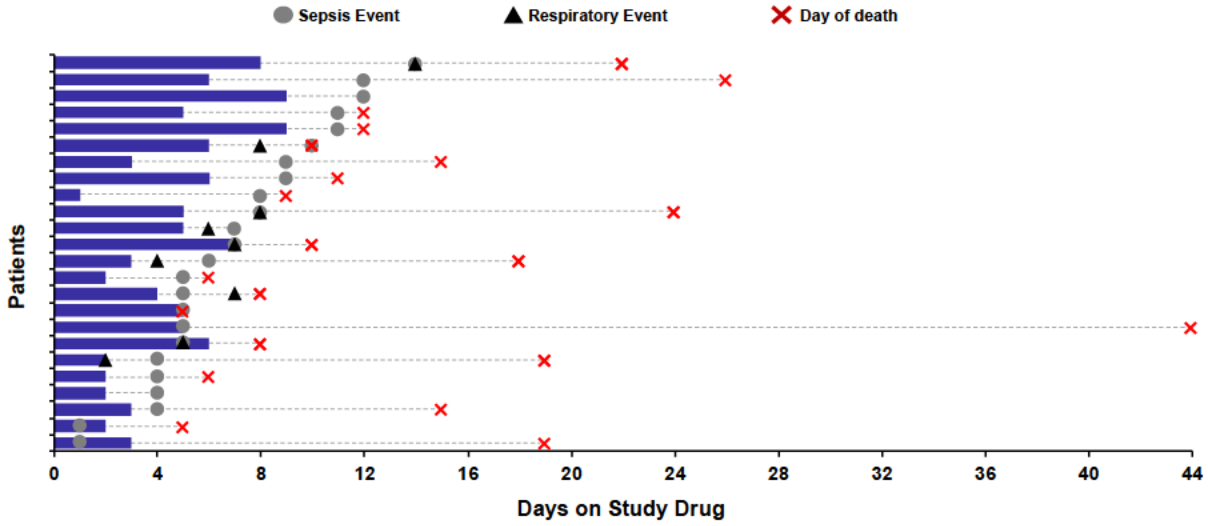
A detailed review of individual subjects with late cases of sepsis indicates that a connection between terlipressin and these cases cannot be established and these late cases are more likely due to underlying decompensated cirrhosis.

Of the 24 terlipressin-treated subjects who experienced sepsis events within 7 days of EOT, 3 developed sepsis following an event of respiratory failure, and 9 developed sepsis following a significant cardiopulmonary event on study, such as pneumonia, pulmonary edema, or pleural effusion (Figure 29). Of the remaining 12 subjects, 2 had a significant history of cardiopulmonary events, 2 had an ongoing infection at baseline, and 6 subjects had an on-treatment infection. The remaining 2 subjects' origin of sepsis is unknown.

Based on the cumulative data available, an effect of terlipressin associated with a risk of developing sepsis/septic shock post-treatment in some patients cannot be excluded.

More than half of the early cases of sepsis involved cardiopulmonary events and may have been mitigated in part by the same measures recommended to mitigate respiratory failure. Section 8.2 provides a detailed discussion of the risk of respiratory failure and the related risk of sepsis in some patients treated with terlipressin, including identification of patients who may be a higher risk for such events and proposed for mitigating these risks.

Figure 29. Subjects With an Early Sepsis AE and a Respiratory AE in the Integrated Phase 3 Terlipressin-Treatment Group (Safety Population)



AE, adverse event.
The blue bars indicate days on study drug and, for those who died, the red X's indicate date of death. The grey circles represent sepsis events that occurred during or within 7 days of the end of study drug treatment and the black triangles indicate respiratory events. Sepsis AEs includes abdominal sepsis, enterococcal sepsis, klebsiella sepsis, septic shock, sepsis syndrome, sepsis, and urosepsis. Respiratory AE includes pneumonia, pulmonary edema, or pleural effusion.

A total of 43 terlipressin-treated subjects (12.3%) and 19 placebo-treated subjects (7.6%) experienced SAEs in the Infections and Infestations SOC (Table 47). None of these SAEs was considered related to study treatment.

Fatal infections reported in the Infections and Infestations SOC occurred in 22 terlipressin-treated subjects (6.3%) and 9 subjects (3.6%) in the placebo group within 30 days from the start of treatment and 29 terlipressin-treated subjects (8.3%) and 10 subjects (4.0%) in the placebo group within 90 days from the start of treatment. Combined sepsis SAEs leading to death were reported in 5.7% of subjects in the terlipressin group compared with 1.6% of the placebo group. Sepsis was the most frequently reported infection-associated AE leading to death up to 30 days post-treatment (11 terlipressin-treated subjects [3.2%] and 3 placebo-treated subjects [1.2%]), followed by septic shock (8 terlipressin-treated subjects [8.3%] and 1 placebo-treated subject [0.4%]).

Table 47. Infections and Infestations Deaths and SAEs in >1 Subject in the Integrated Terlipressin Group by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

Preferred Term[a]	Integrated Phase 3 Studies	
	Terlipressin N=349 n (%)	Placebo N=249 n (%)
Infections and Infestations SAEs	43 (12.3)	19 (7.6)
Sepsis	18 (5.2)	4 (1.6)
Pneumonia	9 (2.6)	8 (3.2)
Septic shock	9 (2.6)	2 (0.8)
Peritonitis bacterial	3 (0.9)	1 (0.4)
Cellulitis	2 (0.6)	1 (0.4)
Enterococcal infection	2 (0.6)	0
Urinary tract infection	2 (0.6)	1 (0.4)
Urosepsis	2 (0.6)	0
Deaths[b] from Infections and Infestations	29 (8.3)	10 (4.0)
Sepsis	13 (3.7)	3 (1.2)
Septic shock	11 (3.2)	1 (0.4)

N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.

a. Subjects experiencing multiple AEs are counted once within the preferred term.

b. Up to 90 days following the start of treatment.

Note: Initial and retreatment periods were combined.

Medical history related to infection was reported for 71.1% and 69.1% of terlipressin-treated and placebo-treated subjects, respectively. During the study, subjects in the integrated terlipressin group had a lower incidence of systemic anti-infectives use (45.6%) compared with subjects in the placebo group (51.4%). The incidences of history of infections and the infection-related AEs fall within the expected range for this patient population (32% to 64%; Fernandez 2002, Borzio 2001, Merli 2010, Das 2010).

Based on the cumulative data available, including detailed review of individual subjects, an association of terlipressin with a risk of developing sepsis/septic shock cannot be excluded.

Sepsis may occur in association with or following cardiopulmonary events; more than half of the early cases of sepsis involved preceding cardiopulmonary events such as pneumonia, pulmonary edema, or pleural effusion. Sepsis may be mitigated in part by the same measures recommended to mitigate respiratory failure.

Careful surveillance for infection should be performed in patients receiving terlipressin and infection should be promptly treated.

7.2.7.8.6 Multiple-Organ Dysfunction Syndrome

MODS, a frequent complication of sepsis, is a progressive dysfunction of ≥2 organ systems. Cirrhotic patients are at high risk for infection and subsequent complications, including SIRS, sepsis, severe sepsis, and MODS, because of impaired immune function, bacterial translocation, and subsequent deterioration of hemodynamic status (Tandon 2008). The most common risk factors for the development of MODS are hypoperfusion without shock, sepsis without shock, and shock regardless of etiology. The clinical manifestations and temporal evolution of organ failure during MODS are influenced by genetic factors and host factors such as advanced age, comorbid diseases, and use of immunosuppressive drugs. For example, patients with cirrhosis, particularly HRS, who become septic, manifest an accelerated evolution of multi-organ failure (MOF) due to impaired hepatic and renal clearance of circulating inflammatory mediators (Siegel 1982, Mizock 2009).

In the integrated studies, a higher incidence of MODS through 7 days post-treatment was seen in terlipressin-treated subjects (5.4%) compared with placebo-treated subjects (3.2%) (Table 48). The incidence of deaths due to MODS reported within 30 days post-treatment and within 90 days from the start of treatment was higher in terlipressin-treated subjects than placebo-treated subjects.

Table 48. Multi-Organ Dysfunction Syndrome AEs by Preferred Term in the Integrated Phase 3 Studies (Safety Population)

	Integrated Phase 3 Studies	
Preferred Term[a,b]	**Terlipressin N=349 n (%)**	**Placebo N=249 n (%)**
MODS AEs	19 (5.4)	8 (3.2)
MODS SAEs	26 (7.4)	8 (3.2)
Deaths from MODS up to 30 days post-treatment	22 (6.3)	8 (3.2)
Deaths from MODS up to 90 days from the start of treatment	25 (7.2)	11 (4.4)

AE, adverse events; MODS, multi-organ dysfunction syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event; SOC, system order class.

a. From the start of study treatment to 7 days after the end of treatment. SAEs were collected up to 30 days after the end of treatment.

b. Subjects experiencing multiple AEs are counted once with the SOC and preferred term.

Note: Initial and retreatment periods were combined.

The events of MODS were evaluated over the course of the development program in order to better understand the apparent imbalance between terlipressin and placebo groups. Evaluation of the data from the REVERSE study led to subsequent clarification of an objective definition for an AE of MODS in this patient population. Investigators were asked to assess baseline CLIF-SOFA scores and ACLF grades. These 2 scoring systems have been well validated in patients with decompensated cirrhosis and HRS-1.

Upon creating a more rigorous, objective definition of MODS, the incidence of AEs of MODS in the CONFIRM study was similar between terlipressin and placebo-treated subjects, with 2.5% experiencing AEs of MODS in the terlipressin group and 3.0% in the placebo group (Table 49).

Table 49. Multi-Organ Dysfunction Syndrome AEs in the Individual Phase 3 Studies (Safety Population)

MODS[a,b]	CONFIRM, n (%)		OT-0401, n (%)		REVERSE, n (%)	
	Terlipressin N=200	Placebo N=99	Terlipressin N=56	Placebo N=55	Terlipressin N=93	Placebo N=95
AEs	5 (2.5)	3 (3.0)	4 (7.1)	0	10 (10.8)	5 (5.3)
SAEs	9 (4.5)	3 (3.0)	5 (8.9)	0	12 (12.9)	5 (5.3)
Deaths from MODS up to 30 days post-treatment	9 (4.5)	3 (3.0)	5 (8.9)	0	8 (8.6)	5 (5.3)

AE, adverse events; MODS, multi-organ dysfunction syndrome; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SAE, serious adverse event.
a. From the start of study treatment to 7 days after the end of treatment. SAEs were collected up to 30 days after the end of treatment.
b. Subjects experiencing multiple AEs are counted once with the system organ class and preferred term.
Note: Initial and retreatment periods were combined.

7.2.7.8.7 Ischemic Adverse Events

Terlipressin is a potent vasoconstrictor, and events such as skin pallor/blanching, local skin necrosis, ischemic bowel, peripheral ischemia, and myocardial ischemia have been reported with terlipressin treatment.

All ischemia-associated AEs were medically reviewed to assess their true potential incidence during treatment and within 24 hours following treatment because of the complexity of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy and the broad organ system manifestations of vasoconstriction and tissue ischemia. In the integrated studies, 25 subjects (7.2%) in the terlipressin group and 1 subject (0.4%) in the placebo group experienced an ischemia-associated AE (Table 50). Ischemia-associated AEs reported by ≥2 subjects in the terlipressin group were skin discoloration (n=6), cyanosis (n=5), intestinal ischemia (n=4),

vascular skin disorder, and ischemia (n=2 each). No cases of skin necrosis were observed in any of the 3 studies.

Ten subjects in the terlipressin group experienced ischemia-associated SAEs, including cyanosis (n=1, 0.3%), intestinal ischemia (n=4, 1.1%), vascular skin disorder (n=2, 0.6%), and livedo reticularis, myocardial infarction, and poor peripheral circulation (n=1, 0.3% each). One subject (0.4%) in the placebo group experienced an ischemia-associated SAE of myocardial ischemia. There were no individual ischemia-associated SAEs with a difference of ≥2% in incidence between the treatment groups. There were no deaths due to ischemia-associated AEs.

In the integrated studies, 13 subjects (3.7%) experienced ischemia-related AEs leading to withdrawal in the terlipressin group (cyanosis [n=3, 0.9%], intestinal ischemia [n=4, 1.1%], vascular skin disorder [n=2, 0.6%], and myocardial infarction, livedo reticularis, skin discoloration, and poor peripheral circulation [n=1, 0.3% each]), compared with 1 subject (0.4%) in the placebo group who withdrew with an ischemia-related AE of myocardial ischemia.

Table 50. Ischemia-Associated AEs up to 24 Hours After Last Dose of Study Drug by SOC and Preferred Term in the Integrated Phase 3 Studies (Safety Population)

	Integrated Phase 3 Studies			
	Terlipressin N=349		Placebo N=249	
System Organ Class Preferred Term[a,b,c]	Subject n (%)	Events n	Subject n (%)	Events n
Ischemia-associated AEs	25 (7.2)	28	1 (0.4)	1
Cardiac Disorders	6 (1.7)	6	1 (0.4)	1
Cyanosis	5 (1.4)	5	0	0
Myocardial infarction	1 (0.3)	1	0	0
Myocardial ischemia	0	0	1 (0.4)	1
Gastrointestinal Disorders	4 (1.1)	4	0	0
Intestinal ischemia	4 (1.1)	4	0	0
Investigations	2 (0.6)	2	0	0
ECG ST segment depression	1 (0.3)	1	0	0
ECG T wave abnormal	1 (0.3)	1	0	0
Skin and Subcutaneous Tissue Disorders	9 (2.6)	9	0	0
Livedo reticularis	1 (0.3)	1	0	0
Skin discoloration	6 (1.7)	6	0	0
Vascular skin disorder	2 (0.6)	2	0	0
Vascular Disorders	6 (1.7)	7	0	0
Ischemia	2 (0.6)	2	0	0
Peripheral coldness	1 (0.3)	1	0	0
Poor peripheral circulation	1 (0.3)	1	0	0

System Organ Class Preferred Term[a,b,c]	Integrated Phase 3 Studies			
	Terlipressin N=349		Placebo N=249	
	Subject n (%)	Events n	Subject n (%)	Events n
Raynaud's phenomenon	1 (0.3)	2	0	0
Vasoconstriction	1 (0.3)	1	0	0

AE, adverse event; ECG, electrocardiogram; N, number of subjects in the treatment group; n; number of subjects in the category of subjects in the treatment group; SOC, system organ class.

a. Subjects were counted only if study drug was received that day. Subjects experiencing multiple episodes of a given preferred term were counted once within each SOC and preferred term.

b. Up to 24 hours after last dose of study drug.

c. Ischemia-associated AEs were determined by medical review of SOC, preferred terms, and reported term.

Note: Initial and retreatment periods were combined.

The incidence of ischemic events observed in the integrated studies was similar to that reported in the literature (4%-13%; Facciorusso 2017, Gluud 2012) and similar to what has been observed in the WHO global pharmacovigilance database. In general, ischemia-associated events are predictable, recognizable, and manageable with dose interruption, followed by dose reduction, or permanent discontinuation of drug, as necessary. In patients who experience signs or symptoms suggestive of ischemic adverse reactions, terlipressin should be temporarily interrupted or permanently discontinued.

7.2.7.9 Assessment of Adverse Events by Baseline SCr

As described in Section 5.5.2, in an effort to optimize the benefit risk for patients who will be treated with terlipressin, we have evaluated the relationship of baseline SCr on the benefits and risks of terlipressin in subgroups of patients with a baseline of <5 mg/dL and ≥5 mg/dL. The incidence of adverse events is high in both treatment groups in the pooled studies; 91.1% and 90.4% for terlipressin and placebo, respectively (Table 31). However, when assessed by baseline SCr, the incidence of severe and serious adverse events, and adverse events leading to death is higher in the terlipressin group compared to placebo in the sub-group with baseline SCr value of ≥ 5.0 mg/dL (Table 51). Importantly, the larger proportion of terlipressin-treated subjects with a fatal AE through Day 30 appears to be driven by higher incidences in the terlipressin group of AEs known to associated with terlipressin treatment, including respiratory failure (Section 7.2.7.8.4), early septic shock (Section 7.2.7.8.5), and MODS (Section 7.2.7.8.6).

Identification of patients most likely to benefit from terlipressin treatment and how the benefit-risk of terlipressin can be optimized based on baseline SCr is described in detail in Section 8.1

Table 51: Overview of Safety Data for the Sub-groups of Subjects with Baseline SCr < 5 mg/dL and ≥5 mg/dL at Baseline by Treatment Group; Pooled Safety Population

	Baseline SCr ≥5 mg/dL		Baseline SCr <5 mg/dL	
	Terlipressin N=44	Placebo N=31	Terlipressin N=305	Placebo N=218
	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)
All Adverse Events	42 (95.5)	29 (93.5)	276 (90.5)	196 (89.9)
Severe Adverse Events	31 (70.5)	12 (38.7)	132 (43.3)	85 (39.0)
Serious Adverse Events	37 (84.1)	17 (54.8)	190 (62.3)	132 (60.6)
Adverse Events leading to Death up to 30 Days post treatment	29 (65.9)	12 (38.7)	116 (38.0)	89 (40.8)
Adverse Events leading to Death up to 90 Days from start of treatment	31 (70.5)	14 (45.2)	138 (45.2)	101 (46.3)

7.2.8 Clinical Laboratory Evaluations

7.2.8.1 Clinical Chemistry

There were no meaningful differences in clinical chemistry findings between the terlipressin- and placebo-treated subjects from the integrated study data for the mean change from baseline values at EOT.

7.2.8.2 Model for End-Stage Liver Disease Score

The MELD is a validated scoring system for cirrhosis that uses a patient's laboratory values for serum bilirubin, SCr, and the INR for prothrombin time to measure the degree of liver and kidney dysfunction in patients with cirrhosis (Wiesner 2001). The MELD score provides a stratification of patients with cirrhosis according to the severity of disease and is used by the UNOS for organ transplant prioritization in US. In the integrated studies, MELD scores improved following terlipressin dosing throughout the study period, with a decrease greater than that seen with placebo dosing at each time point evaluated. From baseline to EOT, the mean MELD score decreased 3 points in the integrated terlipressin group and 1.1 points in the integrated placebo group.

7.2.8.3 Hematology

Hematology results were analyzed over time for CONFIRM and REVERSE only; hematology laboratory specimens were not obtained in OT-0401. The evaluation of mean hematology values over time did not reveal trends or safety concerns in either treatment group in CONFIRM or

REVERSE. A higher incidence of low platelet count in terlipressin-treated subjects compared with placebo-treated subjects was noted in REVERSE, which was not observed in CONFIRM.

7.2.8.4 Laboratory Abnormalities Reported as Adverse Events

In the integrated studies, laboratory-related AEs were reported for 135 (38.7%) terlipressin-treated subjects and 97 (39.0%) placebo-treated subjects. Hypokalemia and anemia were the most frequently reported AEs in the terlipressin group (9.2% and 8.0%, respectively) and also for the placebo group (8.0% and 8.4%, respectively). All other laboratory-related AEs were reported by ≤5% of subjects in the terlipressin or placebo groups, with the exception of metabolic acidosis (terlipressin, 6.3%, placebo, 6.0%).

7.2.9 Vital Signs

7.2.9.1 Blood Pressure

As expected, based on terlipressin's mechanism of action, the mean change from baseline to EOT in systolic blood pressure and diastolic blood pressure was higher for the terlipressin group (6.8 and 3.8 mm Hg, respectively) compared with the placebo group (-1.4 and -1.3 mm Hg, respectively) in the integrated studies. The mean change from baseline to the EOT in MAP was also higher for the terlipressin group (4.8 mmHg) compared with the placebo group (1.4 mm Hg).

7.2.9.2 Heart Rate

The pharmacological effect of terlipressin results in increased MAP triggering a baroflex-induced decreased heart rate (HR). In the integrated safety population, HR decreased slightly from baseline to EOT in the terlipressin group (-0.9 beats/min) compared with the placebo group (3.3 beats/min).

7.2.9.3 Vital Sign Abnormalities Reported as Adverse Events

The most frequently reported vital sign AEs were hypotension (terlipressin, 11.7%; placebo, 7.6%), bradycardia (terlipressin, 6.3%; placebo, 0.8%), and pyrexia (terlipressin, 4.0%; placebo, 5.2%). Bradycardia and hypotension were the only vital sign AEs reported with ≥2% difference between treatment groups (See Section 7.2.7.8.1.1 for a discussion of bradycardia).

7.2.9.3.1 Hypotension

In the integrated studies, AEs of hypotension were reported by 41 subjects (11.7%) in the terlipressin group and 19 subjects (7.6%) in the placebo group. Of these, 7 subjects (2.0%) in the terlipressin group and 4 subjects (1.6%) in the placebo group had events that were considered SAEs, and 1 subject in each group (0.3% and 0.4%, respectively) died from an AE of hypotension. All SAEs were severe events.

Most events of hypotension were mild or moderate in both treatment groups, with 11 subjects (26.2%) and 8 subjects (40.0%) reporting severe events in the terlipressin and placebo groups, respectively. Most of these events were considered by the investigator to be unrelated to the study drug. Causality was deemed as related to the study drug for 8 (19.0%) subjects in the terlipressin group and 2 (10.0%) subjects in the placebo group. No action was taken for most events in both treatment groups, with the study drug being permanently withdrawn for 2 (4.8%) subjects in the terlipressin group and 3 (15.0%) subjects in the placebo group and interrupted for 1 (2.4%) subject in the terlipressin group.

Hypotension is an unusual AE for a vasopressor drug, such that further evaluation was conducted by defining hypotension as a single MAP value of <70 mm Hg or by a series of successive measurements trending downward from 70 mm Hg. The percentage of subjects experiencing a MAP value <70 mm Hg was consistently lower in the terlipressin group compared with placebo through Day 14 post-treatment, and similar to or lower than placebo from Day 14 through the 30-day follow-up. The incidence of subjects with a MAP value <70 mm Hg at EOT was 16.1% in the terlipressin group compared with 18.4% in the placebo group. This observation suggests that the reporting of a low MAP as an AE of hypotension could be related to investigator perceptions of the fluctuating nature of the generally low MAP in patients with decompensated cirrhosis and ACLF. Hypotension in the absence of shock frequently occurs in patients with cirrhosis: 46% of patients with ascites had a MAP ≤80 mm Hg (Llach 1988).

The majority of the events of hypotension in these studies occurred in the setting of other AEs often associated with hypotension, including infections (eg, pneumonia and bacterial peritonitis), MODS, sepsis and septic shock, cardiogenic shock, myocardial infarction, pulmonary edema, hypovolemia, respiratory failure and respiratory distress, metabolic acidosis, and progressive cirrhosis decompensation.

A direct causal association cannot be established between terlipressin administration and hypotension.

7.2.10 Physical Examination Findings

7.2.10.1 QT Interval and Cardiac Repolarization

It was agreed with the FDA at the pre-IND meeting that the potential for QT prolongation could be evaluated in OT-0401 through the collection of paired ECGs at baseline, on study Days 3 and 7 when peak drug concentrations were expected, and EOT or Day 14.

The potential effect of terlipressin to delay cardiac repolarization was evaluated in OT-0401. In addition, cardiac AEs from CONFIRM, OT 0401, and REVERSE were evaluated for cases of QT interval prolongation or torsades de pointes.

In OT-0401, the terlipressin group showed minimal changes from baseline in QT interval. The terlipressin group had a slight increase from baseline in QTcF interval (approximately 8 msec)

compared with the placebo group; however, this relative change from baseline was primarily due to larger decreases in the QTcF interval observed in the placebo group rather than an increase in the terlipressin group.

There were no AE reports of torsades de pointes, sudden death, syncope, or QT interval prolongation in OT-0401. There was 1 case of ventricular tachycardia reported in the terlipressin group and 1case of ventricular fibrillation reported in the placebo group.

In CONFIRM, QT interval data were not collected; only cardiac AE data were collected. A similar incidence of AEs in the Cardiac Disorder SOC was observed for the terlipressin group compared with the placebo group (19.5% vs 17.2%, respectively). The most frequently reported cardiac AEs were tachycardia (5.0%), bundle branch block left (5.0%), and arrhythmia (3.5%) in the terlipressin group and tachycardia (8.1%) and arrhythmia (5.1%) in the placebo group. No AEs of torsades de pointes, sudden death, or syncope were reported in CONFIRM. No subjects in the placebo group and 2 subjects (1.0%) in the terlipressin group were reported to have had QT interval prolongation, both of which were considered unrelated to study drug.

ECG QT interval data were also not collected in REVERSE, only cardiac AE data. The terlipressin group had a higher incidence of AEs in the cardiac disorder SOC compared with the placebo group (23.7% vs 11.6%, respectively). The most frequently reported cardiac AEs were bradycardia (9.7%), cyanosis (3.2%), and atrial fibrillation (3.2%) in the terlipressin group and bradycardia and atrial fibrillation (2.1% each) in the placebo group. No AEs of torsades de pointes, sudden death, syncope, or QT interval prolongation was reported in REVERSE.

Based on the totality of available data evaluated, no causal association between terlipressin administration and QT prolongation in subjects with HRS-1 has been established.

7.2.10.2 Encephalopathy Scores

No meaningful change from baseline in mean or median encephalopathy scores was noted at the EOT in either the terlipressin or placebo groups.

7.3 Safety Conclusions

The safety profile of terlipressin for the treatment of HRS-1 has been thoroughly characterized and supports its use in HRS-1. The events observed in the phase 3 clinical studies are consistent with data available from the WHO database and clinical use outside of the US for more than 10 years for the treatment of HRS-1. Terlipressin was first approved as a pharmaceutical product in Germany in the early 1980s for the treatment of patients with EVH; the HRS indication was added in 2010. The WHO database includes adverse events for any of the approved indications outside the US.

A total of 598 patients were studied in 3 well-controlled phase 3 studies, of whom 349 patients received terlipressin. The majority of AEs reported for terlipressin in the integrated data set were predictable based on the known mechanism of action of the drug, recognizable in the patient

population of those with decompensated cirrhosis, and generally manageable by symptomatic treatment or by reducing or stopping administration of terlipressin.

Consistent with terlipressin's vasoconstrictive effect, events of ischemia were observed; this is manageable with prompt treatment interruption and permanent discontinuation if required.

A causal relationship between terlipressin and a higher incidence of respiratory failure cannot be ruled out. Therefore, it should be used with caution in patients with a prior history of respiratory events or severe respiratory illness.

Physicians should be vigilant to detect and treat infection in HRS patients being treated with terlipressin because of the high incidence of infection and sepsis in this population, which may be increased by the drug.

Terlipressin treatment is not recommended for patients with the most advanced renal dysfunction (ie, baseline SCr greater than approximately 5 mg/dL) because of a higher risk of adverse events and a reduced likelihood of benefit in these highly compromised patients. This, along with the rest of our proposed mitigation strategy, which will involve tools available to the treating physician (eg, proposed labeling, increased education and awareness, and specialty distribution of the drug; Section 8) should lead to a reduction in the key safety risks such as respiratory failure and early sepsis.

8 RISK MITIGATION AND OPTIMIZING THE BENEFIT-RISK OF TERLIPRESSIN TREATMENT IN PATIENTS WITH HRS-1

8.1 Baseline Serum Creatinine

As described in Section 5.5.2, there appears to be an upper limit for baseline SCr above which there is a substantially reduced likelihood of achieving HRS-1 reversal. In our studies, the maximum baseline SCr value recorded for subjects who ultimately achieved HRS-1 reversal was between 5.2 mg/dL and 6.2 mg/dL in the terlipressin group and 4.3 to 5.2 mg/dL in the placebo group (Table 18).

Therefore, in an effort to optimize the benefit risk for patients who will be treated with terlipressin, we sought to evaluate the relationship of baseline SCr on HRS reversal and adverse events and evaluated the benefits and risks of terlipressin in subgroups of patients with a baseline of <5 mg/dL, and ≥5 mg/dL, the value used to define the highest grade of kidney failure within the CLIF-SOFA score.

8.1.1 Benefits

The incidence of HRS-1 reversal is consistently higher with terlipressin compared with placebo in all baseline SCr sub-groups evaluated (Table 52). However, in both treatment groups, subjects with a baseline SCr ≥5 g/dL have a lower incidence of HRS-1 reversal than subjects with a SCr <5 mg/dL. Specifically, in the sub-group of subjects with baseline SCr ≥5 mg/dL, the incidence of HRS-1 reversal is 9.1% in the terlipressin compared to 3.0% in the placebo group; these proportions are substantially lower than for subjects with a baseline SCr <5 mg/dL. The same results were seen in the pivotal CONFIRM study (Table 53).

Table 52: HRS-1 Reversal by Baseline SCr Category, Pooled Analysis (ITT Population)

	Terlipressin		Placebo	
Baseline SCr	**N**	**n (%)**	**N**	**n (%)**
< 3 mg/dL	126	62 (49.2)	84	25 (29.8)
≥ 3 to < 5 mg/dL	182	51 (28.0)	139	16 (11.5)
≥ 5 mg/dL	44	4 (9.1)	33	1 (3.0)

The incidence of HRS-1 reversal is defined as at least one SCr ≤ 1.5 mg/dL on treatment (up to 24 hrs after the last dose of study medication). Any SCr values obtained post-transplant or renal replacement therapy are excluded.
N = number of subjects in the study and treatment group and intrinsic/extrinsic factor.
n = number of subjects with HRS-1 reversal in the study, treatment group and intrinsic/extrinsic factor.

Table 53: HRS-1 Reversal by Baseline SCr Category, CONFIRM Study (ITT Population)

	Terlipressin		Placebo	
Baseline SCr	**N**	**n (%)**	**N**	**n (%)**
< 3 mg/dL	79	29 (36.7)	40	13 (32.5)
≥ 3 to < 5 mg/dL	97	27 (27.8)	53	3 (5.7)
≥ 5 mg/dL	23	2 (8.7)	8	0 (0.0)

The incidence of HRS-1 reversal is defined as at least one SCr ≤ 1.5 mg/dL on treatment (up to 24 hrs after the last dose of study medication). Any SCr values obtained post-transplant or renal replacement therapy are excluded.
N = number of subjects in the study and treatment group and intrinsic/extrinsic factor.
n = number of subjects with HRS-1 reversal in the study, treatment group and intrinsic/extrinsic factor.

8.1.2 Risks

8.1.2.1 Adverse Events

As described in Section 7.2.7.9, when assessed by baseline SCr, the incidence of severe and serious adverse events, and adverse events leading to death is higher in the terlipressin group compared to placebo in the sub-group with baseline SCr value of ≥ 5.0 mg/dL (Table 51).

The overall proportion of subjects with fatal AEs is similar in the subgroup of subjects with a baseline SCr <5 mg/dL (Table 50). However, in subjects with a baseline SCr ≥5 mg/dL, a larger proportion of terlipressin-treated subjects (65.9%) had a fatal AE through Day 30 than placebo-treated subjects (38.7%) (Table 54). Although the overall numbers of subjects in this sub-group are small, this difference between groups appears to be driven by higher incidences in the terlipressin group of fatal AEs of multi-organ dysfunction syndrome (11.4% versus 0% placebo), respiratory failure (4.5% versus 0% placebo), cardio-respiratory arrest (4.5% vs 0% placebo), and septic shock (4.5% vs. 0% placebo). Respiratory failure, early septic shock and, at least in part, MODS are associated with terlipressin therapy.

Table 54: Overall Incidence of Adverse Events Leading to Death by Day 30 for at Least 2 Subjects in either the Terlipressin or Placebo Group by Preferred Term and Baseline SCr Sub-group; Pooled Safety Population

	Baseline SCr ≥ 5 mg/dL		Baseline SCr < 5 mg/dL	
	Terlipressin N=44	Placebo N=31	Terlipressin N=305	Placebo N=218
	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)
Overall	29 (65.9)	12 (38.7)	116 (38.0)	89 (40.8)
Hepatic failure	6 (13.6)	6 (19.4)	14 (4.6)	16 (7.3)
Multi organ dysfunction syndrome	5 (11.4)	0 (0.0)	17 (5.6)	8 (3.7)
Cardio-respiratory arrest	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic hepatic failure	2 (4.5)	1 (3.2)	19 (6.2)	14 (6.4)
Cirrhosis alcoholic	2 (4.5)	1 (3.2)	3 (1.0)	3 (1.4)
Hepatic cirrhosis	2 (4.5)	0 (0.0)	4 (1.3)	2 (0.9)
Hepatorenal syndrome	2 (4.5)	2 (6.5)	5 (1.6)	9 (4.1)
Septic shock	2 (4.5)	0 (0.0)	6 (2.0)	1 (0.5)
Respiratory failure	2 (4.5)	0 (0.0)	15 (4.9)	3 (1.4)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Hepatic encephalopathy	0 (0.0)	0 (0.0)	3 (1.0)	2 (0.9)
Renal failure	0 (0.0)	0 (0.0)	6 (2.0)	3 (1.4)
Respiratory distress	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)
Shock	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.9)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.9)
Procedural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Sepsis	0 (0.0)	0 (0.0)	11 (3.6)	3 (1.4)
Acute kidney injury	0 (0.0)	1 (3.2)	0 (0.0)	1 (0.5)

Subjects experiencing multiple episodes of a given AE are counted once in that preferred term. Initial and retreatment periods are combined.

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.

8.1.2.2 Survival

There is little difference in overall survival (through Day 90) between treatment groups for subjects with a baseline SCr <5 mg/dL. In subjects with a baseline SCr ≥5 mg/dL, overall survival is lower for subjects in the terlipressin group than in the placebo group, in both the pooled data (Table 55 and Figure 30) and the pivotal CONFIRM study (Table 56).

Table 55: Overall Survival up to 90 Days by Baseline Serum Creatinine Category and Treatment Group; Pooled Studies - ITT Population

	Baseline SCr ≥ 5 mg/dL				Baseline SCr < 5 mg/dL			
	Terlipressin		Placebo		Terlipressin		Placebo	
	N	Parameter	N	Parameter	N	Parameter	N	Parameter
Survival Estimate	44	0.292	33	0.469	308	0.545	223	0.514
Median Days of Survival	44	12.0	33	85.0	308		223	
Alive at Day 90 (n, %)	44	13 (29.5)	33	16 (48.5)	308	169 (54.9)	223	117 (52.5)

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.

Figure 30: Overall Survival up to 90 Days by Treatment Group and Baseline SCr (Pooled Studies; Intent-to-treat Population)

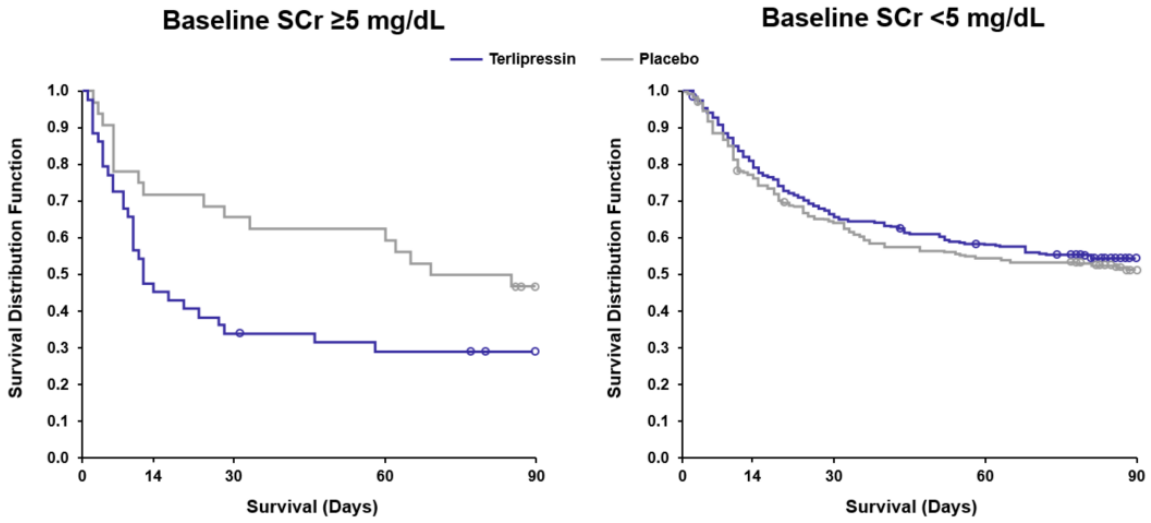
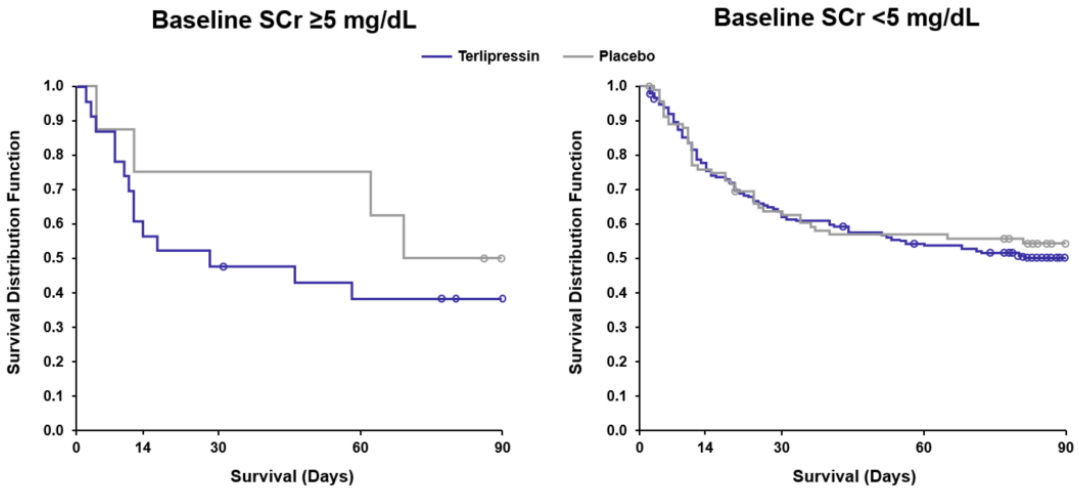


Table 56: Overall Survival up to 90 Days by Baseline Serum Creatinine Categories and Treatment Group; CONFIRM Study - ITT Population

	Baseline SCr ≥ 5 mg/dL				Baseline SCr < 5 mg/dL			
	Terlipressin		Placebo		Terlipressin		Placebo	
	N	Parameter	N	Parameter	N	Parameter	N	Parameter
Survival Estimate	23	0.383	8	0.500	176	0.504	93	0.544
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)

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.

Figure 31: Overall Survival up to 90 Days by Treatment Group and Baseline SCr (CONFIRM; Intent-to-treat Population)



8.1.3 Conclusion

The incidence of HRS-1 reversal is consistently higher in the terlipressin group compared to the placebo group in the two baseline SCr sub-groups evaluated (ie, < 5 mg/dL and ≥5 mg/dL). However, subjects with a baseline SCr ≥5 mg/dL have a lower incidence of HRS-1 reversal versus subjects with serum creatinine values of ≤5 mg/dL regardless of treatment. It also appears that there is an upper limit of SCr between 5.2 and 6.2 mg/dL at which there is a substantially reduced likelihood of achieving HRS-1 reversal and treatment with terlipressin may be of little benefit. By limiting the use of terlipressin in patients with the most advanced renal failure (ie, baseline SCr ≥ 5 mg/dL) and mitigating the key safety risks of respiratory and pulmonary

events, terlipressin, by virtue of restoring renal function and revering HRS, can lower short-term mortality in patients with HRS-1 (Table 66).

In conclusion, clinical trials revealed 3 important findings regarding the benefit-risk of terlipressin in patients with high SCr at baseline:

(1) A notably smaller proportion of patients with SCr ≥5 at baseline experienced HRS-1 reversal

(2) In subjects with baseline SCr ≥5 mg/dL, the risks are higher in the terlipressin group compared to placebo as assessed by severe and serious adverse events, as well as adverse events leading to death.

(3) Overall survival is lower for subjects with SCr ≥5 mg/dL treated with terlipressin compared to placebo

Thus, we believe that reducing exposure to terlipressin in patients with a baseline SCr >5 mg/dL improves the benefit-risk of terlipressin in a majority of patients. For patients with the most advanced renal failure and SCr ≥5 mg/dL treatment with terlipressin is not recommended and initiating terlipressin therapy needs to be carefully considered with regard to potential benefits versus the known risks for this severely compromised population. The decision to use terlipressin in these patients can only be made on a case-by-case basis by the treating physician.

8.2 Respiratory Failure and Related Risks of Sepsis and Death

8.2.1 Risk Identification

Review of the terlipressin clinical database reveals an increased incidence in the proportion of subjects who experienced a serious adverse event of respiratory failure in the terlipressin group, compared with the placebo group, during the clinical development program (Table 57). In addition, an increased incidence of deaths due to respiratory failure is observed in the terlipressin group, compared with the placebo group (Table 58).

Table 57: Incidence of Serious Adverse Events of Respiratory Failure and Acute Respiratory Failure up to 30 Days Post-Treatment in the Pooled Studies (Safety Population)

Preferred Term[a,b]	Terlipressin (N=349) n (%)	Placebo (N=249) n (%)
Respiratory failure	29 (8.3)	6 (2.4)
Acute respiratory failure	11 (3.2)	5 (2.0)

a: Up to 30 days post-treatment.
b: Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.
Note: Initial and retreatment periods are combined.

Table 58: Deaths Due to Respiratory Failure or Acute Respiratory Failure in the Pooled Studies up to 30 Days Post-Treatment (Safety Population)

Preferred Term[a]	Terlipressin (N=349) n (%)	Placebo (N=249) n (%)
Total n (%) with AE leading to death	145 (41.5)	101 (40.6)
Respiratory failure	17 (4.9)	3 (1.2)
Acute respiratory failure	8 (2.3)	2 (0.8)

a: Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.
Note: Initial and retreatment periods are combined.

This imbalance was greatest in the most recent CONFIRM study (Table 59 and Table 60).

Table 59: Incidence of Serious Adverse Events of Respiratory Failure and Acute Respiratory Failure in the CONFIRM Study up to 30 Days Post-Treatment (Safety Population)

Preferred Term[a,b]	Terlipressin (N=200) n (%)	Placebo (N=99) n (%)
Respiratory failure	20 (10.0)	3 (3.0)
Acute respiratory failure	8 (4.0)	2 (2.0)

a: Up to 30 days post-treatment.
b: Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.

Table 60: Deaths Due to Respiratory Failure or Acute Respiratory Failure in the CONFIRM Study up to 30 Days Post-Treatment (Safety Population)

Preferred Terma	Terlipressin (N=200) n (%)	Placebo (N=99) n (%)
Respiratory failure	11 (5.5)	0 (0.0)
Acute Respiratory Failure	6 (3.0)	1 (1.0)

a: Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.

While respiratory failure is an identified risk with terlipressin administration, the incidence in the CONFIRM study was higher than expected based on previous experience from the OT-0401 and REVERSE studies. It is likely that this difference was driven by a shift in clinical practice toward greater use of albumin over the course of the approximately15-year clinical development program, with the highest use observed during the CONFIRM study (Table 61).

Specifically, OT-0401 was conducted based on the 1996 ICA guidelines, which allowed for the use of sodium chloride and/or albumin for fluid challenge. Following the conclusion of OT-0401, the ICA issued revised guidelines (2007) which required albumin use for fluid challenge. Although this revision was issued prior to the start of the REVERSE study in 2011, albumin was still not commonly used in the clinic at the time of the study, primarily due to its high cost, as well the theoretical risk of viral disease transmission (Mirici-Cappa et al, 2011) As additional data became available to support the benefit of albumin treatment in patients with HRS-1, the usage increased, leading to substantially increased mean total albumin use in CONFIRM, which started in 2016, compared with REVERSE (Chasou et al, 2016; Bernardi et al, 2012; Garcia-Martinez et al, 2013).

Table 61: Prior Albumin Use in CONFIRM, REVERSE, and OT-0401 (Safety Population)

	OT-0401		REVERSE		CONFIRM	
	Terlipressin	Placebo	Terlipressin	Placebo	Terlipressin	Placebo
	N=56	N=56	N=97	N=99	N=199	N=101
Overall % of subjects exposed to prior albumin	64.3%	80.0%	100%	100%	99%	99%
Mean total prior albumin exposure (g)	-	-	243.2	218.1	335.0	370.7

Note: mean total prior albumin exposure was not collected in OT-0401.

Patients with decompensated cirrhosis may be fluid overloaded at baseline and may have preexisting cardiovascular and respiratory compromise from cirrhotic cardiomyopathy and

associated diastolic dysfunction, intrapulmonary shunting, decreased intrathoracic volume (from ascites and pleural effusions), anemia, and underlying pulmonary and cardiac diseases. HRS, and associated volume expansion with albumin and intravenous fluids, may exacerbate hypervolemia.

Treatment of HRS with terlipressin, in conjunction with albumin, has been shown to improve renal function compared with albumin alone in patients with HRS. This should facilitate fluid management in hypervolemic patients. However, terlipressin may also increase pulmonary vascular congestion through its effects on cardiac afterload and systemic venous return from its vasoconstrictive effects on arterial pressure and the splanchnic bed, respectively. This may result in pulmonary edema in some treated patients. Moreover, many patients may have hepatic encephalopathy, with impaired airway protection, and experience upper gastrointestinal bleeding and hematemesis, all of which may lead to an increased incidence of aspiration pneumonia. Lastly, increased pulmonary vascular pressures, not necessarily high enough to induce pulmonary edema, may convert low grade pneumonias into florid infiltrates as alveoli become flooded from fluid shifting from the pulmonary capillary bed through an inflamed, more porous interstitium. This problem could be worsened by the effects of terlipressin. It is possible that terlipressin exerts generalized, non-physiologic vasoconstriction in the lungs that interferes with normal, compensatory processes that would otherwise be augmenting blood flow to well ventilated areas and direct it away from poorly ventilated segments.

All of these effects of terlipressin on the respiratory system would be potentiated by the higher doses of albumin used in patients in the CONFIRM trial which could account for the higher rates of events and sequelae in the CONFIRM trial compared with the prior two trials.

8.2.2 Identification of Patients at Increased Risk of Respiratory Events

Prior recent medical history, baseline characteristics, and treatment-emergent cardiorespiratory events were evaluated to identify patients at risk of developing these adverse events. Based on this review, subjects with more advanced decompensated cirrhosis (baseline hepatic encephalopathy ≥ grade 3 [9.4% in terlipressin vs. 6.0% in placebo in the CONFIRM study], ACLF grade 3; Table 62), a significant history of prior, baseline, or treatment emergent events or features (primarily dyspnea, hypotension, pleural effusion, cardiac murmur, hematemesis, wheezing, cardiomegaly, pneumonia/aspiration pneumonia, atelectasis, increasing hepatic encephalopathy, esophageal varices hemorrhage) or recent upper GI hemorrhage appear more likely to develop respiratory failure/acute respiratory failure with terlipressin treatment (Table 63 and Table 64).

Table 62: Baseline Demographics Occurring at a Higher Frequency in Terlipressin-Treated Subjects with Respiratory Failure (Integrated Safety Population)

Preferred Term[a]	Respiratory Failure AE Terlipressin N=46 n (%)	No Respiratory Failure AE Terlipressin N=303 n (%)
Baseline ACLF Grade (n, %)		
0	0 (0.0)	1 (0.3)
1	15 (32.6)	147 (48.5)
2	17 (37.0)	99 (32.7)
3	14 (30.4)	56 (18.5)

Table 63: Prior Medical History AEs Occurring at a Higher Frequency in Terlipressin-Treated Subjects with Respiratory Failure (Integrated Safety Population)

Preferred Term[a]	Respiratory Failure AE Terlipressin N=46 n (%)	No Respiratory Failure AE Terlipressin N=303 n (%)
Dyspnea	15 (32.6)	79 (26.1)
Hypotension	14 (30.4)	62 (20.5)
Pleural effusion	9 (19.6)	43 (14.2)
Gastrointestinal hemorrhage	8 (17.4)	34 (11.2)
Pneumonia	7 (15.2)	32 (10.6)
Atelectasis	7 (15.2)	23 (7.6)
Fluid overload	6 (13.0)	31 (10.2)
Cardiac murmur	6 (13.0)	27 (8.9)
Hematemesis	5 (10.9)	8 (2.6)
Sleep apnea syndrome	4 (8.7)	17 (5.6)
Cardiomegaly	4 (8.7)	6 (2.0)
Esophageal varices hemorrhage	3 (6.5)	12 (4.0)
Hepatic hydrothorax	3 (6.5)	10 (3.3)
Hypervolemia	3 (6.5)	6 (2.0)
Wheezing	3 (6.5)	5 (1.7)
Upper gastrointestinal hemorrhage	2 (4.3)	5 (1.7)
Fluid retention	2 (4.3)	1 (0.3)

a: Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.
Note: Initial and retreatment periods are combined. Respiratory failure includes respiratory failure and acute respiratory failure and is up to 90 days from the start of treatment.

Table 64: Treatment-Emergent AEs Occurring at a Higher Frequency in Terlipressin-Treated Subjects with Respiratory Failure (Integrated Safety Population)

Preferred Term[a]	Respiratory Failure AE Terlipressin N=46 n (%)	No Respiratory Failure AE Terlipressin N=303 n (%)
Hepatic encephalopathy	7 (15.2)	21 (6.9)
Pneumonia aspiration	4 (8.7)	0
Encephalopathy	2 (4.3)	4 (1.3)
Hematemesis	2 (4.3)	1 (0.3)

a: Subjects experiencing multiple episodes of a given adverse event were counted once with each preferred term.
Note: Initial and retreatment periods are combined. Respiratory failure includes respiratory failure and acute respiratory failure and is up to 90 days from the start of treatment.

These data support the conclusion that dyspnea, hepatic encephalopathy, upper GI bleeding, atelectasis, and aspiration pneumonia, in the setting of hypervolemia and preexisting cardiovascular and respiratory disease, account for much of the increased incidence, and increased severity, of respiratory failure observed in terlipressin-treated subjects.

8.2.3 Mitigation of Respiratory Failure and Related Respiratory and Sepsis Events and Death

It is possible that the incidence of respiratory failure observed in the terlipressin clinical program could be favorably impacted by a mitigation strategy designed to reduce the proportions of patients who progress to respiratory failure. As the Sponsor has observed that events of sepsis may complicate events of respiratory failure or other pulmonary disorders, especially pneumonia, a mitigation strategy directed at decreasing the incidence of respiratory failure might also mitigate the risk for events of sepsis, including those leading to death. The reason for the association between respiratory disorders, especially respiratory failure, and sepsis is not clear. It may primarily be the result of the spread of bacteria from areas of pneumonia to the blood and other organs, although in some cases it could reflect the systemic effects of hypoxia and acidemia resulting from impaired gas exchange on the integrity of the intestinal mucosa and bacterial translocation into the blood.

We propose the following mitigation guidance to help identify those patients who may be at greater risk and to reduce the likelihood of progression to severe respiratory events, which may be complicated by associated events of sepsis and can lead to death:

- Patients with new onset or worsening dyspnea, tachypnea, or significant respiratory disease should be stabilized prior to receiving terlipressin. This includes managing fluid overload and pneumonia.

- Treatment with terlipressin is not recommended in patients with serum creatinine ≥ 5.0 mg/dL.
- Fluid overload should be managed by decreasing the administration of albumin and other fluids and judicious use of diuretics. If pneumonia occurs or progresses, or pulmonary edema is severe, terlipressin dosing should be interrupted, reduced, or discontinued.
- Patients with hepatic encephalopathy ≥3 are at increased risk for aspiration. Hepatic encephalopathy should be treated and the airway should be protected as clinically indicated prior to initiating terlipressin.

8.2.3.1 Expected Impact of Mitigation

A retrospective analysis assessed the impact of the mitigation strategy on respiratory events and their sequelae, by applying it to the clinical trial data to determine how much it might have reduced incidences of respiratory failure, sepsis, and death in subjects treated with terlipressin.

CONFIRM Study

Based on retrospective review of the clinical data from 27 subjects in the terlipressin group with a serious adverse event of respiratory failure or acute respiratory failure, 17 subjects (63.0%) might have avoided the event had the proposed mitigation strategy been in place (Table 65).

Five of the subjects would not have been enrolled into the trial and exposed to terlipressin and albumin therapy. Three of these subjects had instability of underlying pulmonary disease: a subject with increasing oxygen requirement just prior to the initiation of terlipressin therapy who developed respiratory failure after only a single infusion; a subject with COPD exacerbation and ongoing hypercapnia and hypoxia who experienced respiratory failure on Day 4; and a subject with dyspnea requiring treatment with inhalational therapy prior to enrollment who had onset of acute respiratory failure after the second terlipressin dose. An additional 2 subjects had baseline serum creatinine values of 5.1 mg/dL and 5.7 mg/dL, and would not have been eligible for enrollment into the trial under the proposed mitigation guidelines.

An additional 3 subjects who developed worsening or new onset of pulmonary disease (one each of new onset dyspnea, pneumonia and worsening tachypnea), and 4 subjects who experienced pulmonary edema while on terlipressin therapy, would have had their terlipressin regimen adjusted, at least temporarily, according to the proposed mitigation guidelines. Finally, 5 subjects with hepatic encephalopathy ≥ grade 3 at either baseline or during treatment who subsequently developed pneumonia or infiltrates, would have either had their mental status improved or their airways adequately protected prior to either the initiation or continuation of terlipressin therapy.

With regard to mortality, 10 of the 17 subjects in the terlipressin group with serious respiratory failure or acute respiratory failure who died from respiratory failure or acute respiratory failure within 30 days of the end of treatment had potentially mitigatable factors. This includes 3 subjects with baseline instability of respiratory status and 1 subject with hepatic encephalopathy

prior to enrollment, 3 subjects with treatment-emergent pulmonary edema, a subject with treatment-emergent worsening tachypnea, and 2 subjects with baseline serum creatinine ≥5.0 mg/dL). An additional subject who developed respiratory failure and was continued on terlipressin therapy progressed to hypoxemic, hypercarbic respiratory failure requiring mechanical ventilation prior to succumbing to respiratory failure. These findings show that 64.7% (11 of 17) of subjects who had a fatal event of respiratory failure or acute respiratory failure may have had the event mitigated.

Eleven subjects in the terlipressin group experienced an event of sepsis, septic shock or urosepsis within 7 days of the end-of-treatment. Two of these subjects also had a serious event of respiratory failure or acute respiratory failure that might have been mitigated by the proposed strategy. An additional 4 subjects who did not experience a serious respiratory failure event, but did develop treatment-emergent evidence of pulmonary disease (non-serious respiratory failure; increasing infiltrates and pulmonary hemorrhage; dyspnea on exertion and tachypnea; and hypoxia) during treatment that would have been addressed by the mitigation strategy, subsequently developed sepsis or septic shock. This finding involving 6 of the 11 subjects (54.5%) in the trial with a sepsis event suggests that the proposed mitigation strategy for respiratory failure could have impacted the incidence of sepsis in the CONFIRM study as well.

Table 65: Proposed Mitigation Strategy Could Have Reduced Total Respiratory Failure SAEs and Associated Fatal Outcomes by > 60%

Mitigation	Potential Number of Total SAEs Mitigated in CONFIRM	Potential Number of Fatal SAE Outcomes Mitigated in Confirm
Patients with new-onset or worsening dyspnea, tachypnea, or significant respiratory disease should be stabilized prior to receiving terlipressin. This includes managing fluid overload and pneumonia.	6	5
Treatment with terlipressin is not recommended in patients with baseline SCr ≥ 5 mg/dL.	2	2
Fluid overload should be managed by decreasing the administration of albumin and other fluids and judicious use of diuretics. If pneumonia occurs or progresses, or pulmonary edema is severe, terlipressin dosing should be interrupted, reduced, or discontinued.	4	3
Patients with hepatic encephalopathy ≥ 3 are at an increased risk for aspiration. Hepatic encephalopathy should be treated and the airway should be protected as clinically indicated prior to initiating terlipressin	5	1
Total Mitigation Impact	17/27	11/17

OT-0401 and REVERSE Studies

Retrospective review of respiratory and acute respiratory failure events and deaths in the OT-0401 and REVERSE studies supports the finding of the CONFIRM study analysis and the potential impact on both the incidence of respiratory failure and acute respiratory failure adverse events and deaths, and sepsis events.

Of the 13 subjects in the terlipressin groups with serious respiratory failure or acute respiratory failure in these 2 studies, the proposed mitigation strategy might have prevented the event in 7 subjects (53.8%). This includes four subjects who would not have been enrolled into the studies (one subject each with new dyspnea on exertion and wheezing; pulmonary edema; pneumonia; and baseline serum creatinine ≥ 5.0 mg/dL), one subject with hepatic encephalopathy ≥ grade 3 at baseline, and 2 subjects with treatment-emergent pulmonary disease (one subject each with pulmonary edema and bronchopneumonia). Of the 8 subjects who died of respiratory failure or acute respiratory failure within 30 days of the end-of-treatment, 4 (50%) had potentially mitigatable events (the subjects with pulmonary edema and hepatic encephalopathy ≥ grade 3 at baseline, and the subjects with treatment-emergent pulmonary edema and bronchopneumonia).

Thirteen subjects in the terlipressin groups of OT-0401 or REVERSE experienced an event of sepsis, septic shock or sepsis syndrome within 7 days of the end-of-treatment. Of these subjects, 7 (53.8%) had respiratory events that might have been subject to mitigation: 5 with serious respiratory failure or acute respiratory failure, one with pulmonary edema, and one with pulmonary edema and pneumonia. This supports the findings in CONFIRM that the proposed mitigation strategy for respiratory failure could also have mitigated events of sepsis had it been in place during the studies.

Mortality in the Pooled Safety Population

When mortality through Day 90 was analyzed for the pooled safety population, after removing fatal events that would have been possibly mitigated by the proposed mitigation strategy, results show a potential, meaningful impact of the strategy on decreasing mortality in the terlipressin group. The incidence of deaths with this analysis was lower in the terlipressin group during the treatment period and at all subsequent time points through Day 90 (Table 66).

Table 66: Impact of Proposed Mitigation on Mortality Through Day 90 - Pooled Analysis; Safety Population

	Terlipressin (N = 278) n (%)	Placebo (N = 218) n (%)
Death[a] During Study Treatment Period	6 (2.2)	10 (4.6)
Death by Day 7	20 (7.2)	25 (11.5)
Death by Day 14	49 (17.6)	51 (23.4)
Death by Day 30	82 (29.5)	77 (35.3)
Death by Day 60	102 (36.7)	98 (45.0)
Death by Day 90	113 (40.6)	104 (47.7)
Death at any Time During the Study[b]	115 (41.4)	104 (47.7)

a: Date of death is used to determine timing

b: Excludes death after 90 days when the date of death is known. Subjects (b) (6), (b) (6) do not have death dates but are confirmed as dead

Summary

Based upon retrospective analyses of safety data from the terlipressin clinical program, the proposed mitigation strategy could potentially have decreased respiratory failure and acute respiratory failure events and deaths by more than 60% in terlipressin-treated subjects. Because of the association of sepsis events with respiratory failure or other pulmonary disorders, the mitigation strategy for respiratory failure could have also reduced the incidence of early sepsis (within 7 days of the end-of-treatment) by more than 50%. As about 60% of the events of sepsis occurred early in, during, or within 7 days following treatment, an overall decrease in sepsis events of about 30% might have been observed in the clinical program had the proposed mitigation strategy been incorporated. A relationship between later sepsis events and terlipressin is difficult to establish and most likely reflects the known risks for infection in patients with underlying decompensated liver disease. Importantly, by limiting use in patients with the most advanced renal failure (ie, baseline SCr $\geq$ 5 mg/dL) who have high 90-day mortality regardless of response to treatment, terlipressin, by virtue of restoring renal function and revering HRS, can lower short-term mortality in patients with HRS-1.

8.2.3.2 Proposed Risk Mitigation Actions

The Sponsor will work with the FDA to ensure the appropriate information is captured in the final labeling to ensure the mitigation steps are aligned and adequately communicated. In addition, the Sponsor will be developing a robust communication plan that captures additional measures such as educational materials, risk communications, and measures of effectiveness to ensure adequate training is provided to health care professionals.

We intend to mitigate the potential risks of respiratory failure, which may be complicated by associated events of sepsis and can lead to death, by providing detailed product labeling that will inform healthcare providers of these potential risks in specific patient populations. In addition to labeling, we propose the implementation of a comprehensive education program in multiple formats for healthcare providers and institutions that are expected to be involved in the treatment of HRS-1 with terlipressin. The education program is proposed to include a communication to healthcare providers and institutions, highlighting the label recommendations on appropriate patient selection and the risks associated with the use of terlipressin, including the risk of respiratory failure and associated risks of sepsis and death. We will evaluate the effectiveness of the education program on a regular basis and make adjustments as necessary.

Pharmacovigilance activities will involve monitoring events from the global safety database as well as enhanced pharmacovigilance activities for events of special interest and the use of a health care provider named-patient questionnaire. The questionnaire will be focused on the targeted, structured collection of additional data on the events of special interest associated with terlipressin following market authorization. Pharmacovigilance activities will also include periodic signal detection activities with a targeted focus to monitor known risks (eg, ischemic and respiratory events) and the evaluation of any potential new and evolving signals. Aggregate periodic safety reporting will be performed to confirm the safety profile and monitor the benefit risk profile of terlipressin for injection.

9 BENEFIT-RISK

Terlipressin is an important therapeutic option that addresses an unmet medical need. The efficacy and safety data support a favorable benefit-risk assessment for the treatment of adult patients with HRS-1.

HRS-1 is a rare, functional renal failure complicating decompensated cirrhosis. There is no approved pharmacological treatment for HRS-1 in the US.

Terlipressin provides short-term, in-hospital treatment to address the acute renal dysfunction associated with HRS-1. It is the only drug to have demonstrated a durable benefit in double-blind, randomized, placebo-controlled studies in patients with HRS-1.

The main goals of treatment are acute improvement in renal function and reversal of the hemodynamic pathophysiology of HRS-1. Treatment with terlipressin accomplishes these goals by decreasing splanchnic vasodilation and thereby improving renal hemodynamics, ameliorating afferent renal vasoconstriction, and improving GFR. The placebo-controlled studies consistently show improvements in SCr, a direct measure of renal function. These translate to clinically meaningful improvements, including reduced RRT, shorter ICU stays, and better survival outcomes post-transplant.

9.1 Demonstrated Benefits

The results of the pivotal phase 3 study CONFIRM and the supportive OT-0401 study demonstrate that terlipressin administered as an IV bolus of 1-2 mg q6h plus albumin is superior to placebo plus albumin for achieving sustained reversal of HRS-1 and improvement of renal function, as shown by the incidence of HRS Reversal and a significant decrease in SCr from baseline to EOT.

CONFIRM showed a statistically significant and clinically relevant effect of terlipressin, with a larger proportion of terlipressin-treated subjects than placebo-treated subjects achieving Verified HRS Reversal (29.1% and 15.8%, respectively; p=0.012).

The re-analysis of OT-0401 provides supportive evidence of efficacy. Although this study did not achieve its primary endpoint, Treatment Success at Day 14, in the prespecified analysis, statistical significance was achieved in a re-analysis that included all available post-treatment SCr data. This approach was prospectively agreed upon with the FDA.

The primary endpoint in REVERSE, confirmed HRS Reversal, did not reach statistical significance; however, the results numerically favored terlipressin for the primary endpoint and all secondary endpoints, including improvement in overall renal function compared with placebo.

The pooled analysis of the 3 phase 3 studies also supported the benefits demonstrated in CONFIRM. CONFIRM and the pooled analysis showed a reduced incidence and frequency of

RRT on terlipressin. This is particularly important in vulnerable patients with decompensated liver disease who often have complications during and after dialysis, including a higher rate of bleeding events. Reducing the incidence of RRT also benefits the healthcare system. Overall, reversal of renal failure simplifies patient management, with less utilization of resources, such as shorter ICU stays (Allegretti 2018). In the CONFIRM study, the mean length of ICU stay for terlipressin-treated patients was less than half of that for placebo-treated patients, 6.4 vs 13.5 days, respectively.

In patients with a complex interplay of comorbidities, having 1 fewer complication is a valuable outcome. For the majority of HRS-1 patients who are not candidates for a liver transplant, reversing HRS-1 and restoring improving renal function facilitates medical management of their overall condition. Restoring renal function also allows time to address other potentially reversible complications, such as alcoholic hepatitis (Wong 2015). By limiting use in patients with the most advanced renal failure (ie, baseline SCr ≥ 5 mg/dL) who have high 90-day mortality regardless of response to treatment, terlipressin, by virtue of restoring renal function and revering HRS, can lower short-term mortality in patients with HRS-1 (Table 66).

Improving renal function pre-transplant results in better post-transplantation outcomes in patients who have a liver transplant, including lower rates of RRT post-transplant and higher overall survival (Sanyal 2008, Zand 2011, Gluud 2012, Hiremath 2013, Boyer 2016, Zheng 2017, Wang 2018). In both the CONFIRM study and the pooled efficacy analysis of the 3 phase 3 studies, terlipressin treatment was associated with improved clinical outcomes compared with placebo in the key subgroup of subjects who received liver transplants.

The benefit of terlipressin treatment was further analyzed in 3 important subgroups: subjects with alcoholic hepatitis, subjects with SIRS, and subjects with low MAP at baseline. There was a higher incidence of HRS-1 Reversal with terlipressin treatment in all 3 of these difficult-to-treat subgroups, 3-7-fold higher than that seen in the placebo group. Subjects in these subgroups also had lower incidence of RRT with terlipressin.

Overall, terlipressin has shown durable and clinically meaningful benefit in the acute treatment of HRS-1. Efficacy and safety results support the recommended dosing regimen of 1 mg q6h (4 mg/day) increased to 2 mg q6h on Day 4 (after a minimum of 10 doses), if required.

9.2 Demonstrated Risks

Terlipressin has a well-established safety profile from the clinical studies and the extensive post-marketing experience outside the US. Adverse events experienced by patients treated with terlipressin are predictable, recognizable, and generally manageable by symptomatic treatment or by reducing or stopping administration.

HRS-1 is a serious disease with a high incidence of mortality. In the integrated safety analysis derived from the 3 phase 3 clinical studies, mortality was similar in the 2 groups, with most deaths due to chronic hepatic failure.

Most of the AEs seen with terlipressin are consistent with ex-US labeling and are generally expected based on the mechanism of action. The potential risks associated with the use of terlipressin include ischemic events, GI events, respiratory events, infections, cardiac events, and fetal harm when used in pregnancy.

Ischemic events are an expected risk for terlipressin-treated patients. These events are consistent with the vasoconstrictive action of terlipressin (Kiska-Kanowitz 2004, Narahara 2009, Krag 2010). In the clinical studies, all ischemic events were nonfatal and manageable with temporary interruption or discontinuation of terlipressin treatment, if needed. The incidence of ischemic events observed in the phase 3 studies was similar to that reported in the literature (Gluud 2012, Facciorusso 2017). Terlipressin should be used with caution in patients with a history of ischemic events.

Gastrointestinal AEs, including abdominal pain, vomiting, and diarrhea, were the most frequently occurring AEs reported in terlipressin-treated subjects across the 3 studies. Like ischemic events, GI events are expected based on the mechanism of action and are generally manageable symptomatically or with dose reduction.

Respiratory disorders are frequently seen in patients with decompensated cirrhosis and constitute a known risk associated with the use of terlipressin. In the clinical studies, there was a higher risk of respiratory failure in patients with more advanced disease, a history of cardiorespiratory events, or recent upper GI hemorrhage. Terlipressin should be used with caution in these patients, and the dose should not be increased in those with treatment-emergent cardiorespiratory events. Patients with respiratory symptoms should be evaluated for pulmonary edema. If fluid overload is observed, a reduction in albumin dose and short-term diuretic therapy may be in order. If symptoms persist, further management may include dose reduction or temporary interruption of terlipressin dosing.

There was a higher incidence of sepsis and septic shock with terlipressin compared with placebo. Sepsis, septic shock, and other bacterial infections are common complications of decompensated cirrhosis, and septic shock is a frequent cause of death in patients with cirrhosis and decompensated cirrhosis, including those with HRS-1. An effect of terlipressin associated with a risk of developing sepsis/septic shock in some patients cannot be excluded. The majority of sepsis/septic shock events in the terlipressin group of the integrated safety analysis occurred after treatment, most often after ≥8 days. More than half of the earlier cases of sepsis involved recent cardiopulmonary events such as pneumonia, pulmonary edema, or pleural effusion. The risk of sepsis may be mitigated in part by the same measures recommended to prevent respiratory

failure in patients receiving terlipressin. These patients should also be monitored carefully for infection and treated promptly should infection occur.

Patients with the most advanced renal dysfunction (ie, baseline SCr ≥ 5mg/dL) have a lower likelihood of achieving HRS-1 reversal, experience a higher incidence or severe, serious, and/or fatal AEs, and have a higher 90-day mortality. Thus, in order to optimize the benefit-risk of terlipressin, terlipressin use is not recommended in these highly compromised patients.

Based on its mechanism of action, terlipressin may cause fetal harm when administered to pregnant women. If terlipressin is used during pregnancy, or if the patient becomes pregnant while receiving terlipressin, they should be apprised of this risk.

9.3 Quantitative Benefit-Risk Evaluation

In deciding treatment for the individual HRS-1 patient, the overall benefit-risk profile of terlipressin must be considered in terms of the likelihood of benefit versus the potential for harm. Based on placebo-corrected numbers from the clinical trials, it is possible to predict how many patients treated with terlipressin would benefit over albumin alone, and weigh these against the potential serious harms (SAEs) terlipressin could cause over albumin alone. The benefits are clear in terms of HRS reversal and improved kidney function, as reflected in lower SCr and reduced need for RRT, including reduced RRT use post-transplant (Table 67).

Because of the serious nature of respiratory failure and sepsis, it is also important to consider the impact of risk mitigation strategies in making an evidence-based decision for an individual patient. Based on the review of clinical trial data, applying the mitigation strategy described in Section 9 would reduce the number of serious respiratory failure events by more than 60%, and the number of serious sepsis events by approximately 30%. This would have a favorable impact on the NNT analyses for respiratory failure and early sepsis events as indicated in Table 68. By incorporating the recommendation against use in the population of patients with a baseline SCr ≥5 mg/dL, this not only improves the survival estimate as shown in Section 8.1.2.1, but it also results in lower NNTs for avoidance of RRT, also reflected in Table 67. While this is an important recommendation for optimizing the overall benefit/risk ratio, it is imperative that the treating physician have the ability to make this choice for each patient, based on access to approved and effective treatment and on individual benefits and risks.

Table 67: Number Needed to Treat (NNT) for Benefits and Harms of Terlipressin Treatment; Integrated Studies (Intent-to-treat Population)

NNT for Benefit		NNT for Harm	
HRS Reversal	6	Ischemic SAE[c]	89
No RRT by Day 30[a]	17	Respiratory failure SAE[c]	13
No RRT post-transplant[a,b]	22	Sepsis SAE ≤7 days post-treatment[c]	20

HRS, hepatorenal syndrome; NNT, number needed to treat; RRT, renal replacement therapy; SAE, serious adverse event; ITT, intention-to-treat population

a: For "No RRT by Day 30," REVERSE only captures yes/no if there was an RRT by these follow-up days. This information is used since there are no RRT dates for the time periods. For "No RRT post-transplant," if a subject is retreated, RRT can occur during the initial or retreatment period. Additionally, for REVERSE, if RRT is during the
followup period, then it is captured as yes/no for day 30, 60, and 90 visit. In these cases, RRT date is assigned as the last visit date +1.

b: Subset of subjects receiving a transplant of the ITT population.

c: Initial and retreatment periods are combined for AEs.

Table 68: Number Needed to Treat (NNT) for Benefits and Harms of Terlipressin Treatment Applying Mitigation Strategy; Integrated Studies (Intent-to-treat Population)

NNT for Benefit		NNT for Harm	
HRS Reversal	6	Ischemic SAEc	71
No RRT by Day 30a	14	Respiratory failure SAEc	64
No RRT post-transplanta,b	19	Sepsis SAE ≤7 days post-treatmentc	39

HRS, hepatorenal syndrome; NNT, number needed to treat; RRT, renal replacement therapy; SAE, serious adverse event; ITT, intention-to-treat population

a: For "No RRT by Day 30," REVERSE only captures yes/no if there was an RRT by these follow-up days. This information is used since there are no RRT dates for the time periods. For "No RRT post-transplant," if a subject is retreated, RRT can occur during the initial or retreatment period. Additionally, for REVERSE, if RRT is during the
followup period, then it is captured as yes/no for day 30, 60, and 90 visit. In these cases, RRT date is assigned as the last visit date +1.

b: Subset of subjects receiving a transplant of the ITT population.

c: Initial and retreatment periods are combined for AEs.

9.4 Benefit-Risk Conclusions

The overall benefit-risk profile of terlipressin as an acute therapy for HRS-1 is favorable.

HRS-1 is an acute functional renal failure in patients already seriously ill with decompensated cirrhosis. If not reversed rapidly, this severe complication will progress to permanent renal failure on top of the existing advanced liver disease.

Terlipressin is a short-term therapy that improves renal function and reverses HRS-1. The benefits of terlipressin treatment are durable and clinically meaningful. The risks are well characterized, predictable, recognizable, and generally manageable, particularly as terlipressin is used only in-hospital in patients who are already closely monitored because of their decompensated liver disease. The proposed respiratory failure mitigation strategy combined with the recommendation not to treat patients with a baseline SCr ≥5 mg/dL will likely further enhance the favorable benefit-risk profile of terlipressin. The respiratory failure mitigation should reduce events of respiratory failure and early sepsis and associated mortality. The serum creatinine recommendation should further reduce fatal events and increase the proportion of patients avoiding RRT.

Terlipressin is the standard-of-care for HRS-1 in all of the countries where it is approved. It has been used successfully in Europe and elsewhere for >10 years for the treatment of HRS-1. Until now, sufficient clinical study data were not available to support approval in the US. With the recently completed CONFIRM study, there is compelling evidence for terlipressin use.

HRS-1 patients in the US deserve access to this important medication. The majority of patients who develop HRS-1 in the US do not receive a liver transplant and have no viable, effective, FDA approved, and proven treatment option. There is a clear medical need to make terlipressin available to improve care for these vulnerable patients.

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11 APPENDIX 1: HRS REVERSAL BY INTRINSIC AND EXTRINSIC FACTORS IN THE POOLED ITT POPULATION

Table 69. HRS Reversal by Intrinsic and Extrinsic Factors (Pooled ITT)

	Terlipressin		Placebo	
	N	n (%)	N	n (%)
Age, y				
<65	298	100 (33.6)	220	36 (16.4)
≥65	54	17 (31.5)	36	6 (16.7)
Sex				
Male	213	73 (34.3)	165	25 (15.2)
Female	139	44 (31.7)	91	17 (18.7)
Race				
White	313	108 (34.5)	235	40 (17.0)
Non-white	35	8 (22.9)	20	2 (10.0)
Geographic region				
United States	313	97 (31.0)	228	38 (16.7)
Canada	26	15 (57.7)	16	2 (12.5)
Baseline alcoholic hepatitis				
Present	121	46 (38.0)	84	11 (13.1)
Not Present	231	71 (30.7)	172	31 (18.0)
Baseline MELD score[a]				
Low MELD score	145	63 (43.4)	101	20 (19.8)
High MELD score	167	40 (24.0)	120	17 (14.2)
Baseline CPT score				
Class A [5-6]	5	3 (60.0)	3	1 (33.3)
Class B [7-9]	100	39 (39.0)	71	14 (19.7)
Class C [10-15]	232	72 (31.0)	168	26 (15.5)
Baseline MAP, mm Hg				
<65	49	11 (22.4)	34	2 (5.9)
≥65	303	106 (35.0)	221	40 (18.1)
Dose level[b]				
High dose	95	38 (40.0)	86	20 (23.3)
Low dose	253	79 (31.2)	164	22 (13.4)

Table 69. HRS Reversal by Intrinsic and Extrinsic Factors (Pooled ITT)

	Terlipressin		Placebo	
	N	n (%)	N	n (%)
Prior midodrine and octreotide use				
Yes	147	59 (40.1)	91	15 (16.5)
No	205	58 (28.3)	165	27 (16.4)
Prior vasopressor use				
Yes	183	72 (39.3)	123	23 (18.7)
No	169	45 (26.6)	133	19 (14.3)
Concomitant beta-blockers				
Beta-blockers	71	25 (35.2)	57	11 (19.3)
No beta-blockers	281	92 (32.7)	199	31 (15.6)
Concomitant treatment of alcoholic hepatitis				
Treatment for alcoholic hepatitis	60	23 (38.3)	37	8 (21.6)
No treatment for alcoholic hepatitis	292	94 (32.2)	219	34 (15.5)
Concomitant albumin				
Albumin	300	102 (34.0)	231	38 (16.5)
No albumin	52	15 (28.8)	25	4 (16.0)
Total doses of exposure range, n				
≤10 Doses	98	4 (4.1)	70	0 (0.0)
>10 Doses	250	113 (45.2)	180	42 (23.3)
≤2 Doses	145	6 (4.1)	125	2 (1.6)
>2 Doses	203	111 (54.7)	125	40 (32.0)

CPT, Child-Pugh-Turcotte; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, model end-stage liver disease; N, number of subjects in the study and treatment group and intrinsic/extrinsic factor; n, number of subjects with HRS Reversal in the study, treatment group and intrinsic/extrinsic factor; SCr, serum creatinine.
a. The median MELD score determines high/low MELD score. A low MELD score is <34. A high MELD score is ≥34.
b. Subjects in the standard dose level received only 0.5- and 1-mg doses. Subjects in the high dose level received ≥1 dose ≥2 mg.