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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Terlipressin-containing medicinal products indicated in the treatment of hepatorenal syndrome

Procedure number: EMEA/H/A-31/1514

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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List of abbreviations

ACLF	Acute-on-chronic liver failure
AE	Adverse event
AKI	Acute kidney injury
CI	Confidence interval
EASL	European Association for the Study of the Liver
FDA	U.S. Food and Drug Administration
HRS	Hepatorenal syndrome
HRS-AKI	Hepatorenal syndrome with acute kidney injury (HRS-1)
HRS-NAKI	Hepatorenal syndrome with non-acute kidney injury (HRS-2)
ICA	International Club of Ascites
ICU	Intensive care unit
IQR	Interquartile range
ISS	Integrated summary of safety
IV	Intravenous
K-M	Kaplan-Meier
MAH	Marketing authorisation holder
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end-stage liver disease
PL	Package leaflet
PSUSA	Periodic safety update report single assessment
RCT	Randomised controlled trial
RD	Risk difference
RMM	Risk Minimisation Measure
RR	Relative risk
RRT	Renal replacement therapy
SAE	Serious adverse event
sCR	Serum creatinine
SIRS	Systemic inflammatory response syndrome
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Queries

SMQ	Standardised MedDRA Query
SOC	MedDRA system organ class
Type 1 HRS	Type 1 hepatorenal syndrome corresponding to HRS-AKI
Type 2 HRS	Type 2 hepatorenal syndrome corresponding to HRS-NAKI
UK	United Kingdom
USA	United States of America
V1 receptor	Vasopressin receptor type 1

1. Information on the procedure

New safety data from the CONFIRM trial (Wong et al, 2021) were identified in the last Periodic safety update report single assessment (PSUSA) procedure (PSUSA/00002905/202104) for terlipressin-containing medicinal products concluded in December 2021 by PRAC. In this trial, despite a significantly increased effect on type 1 hepatorenal syndrome (type 1 HRS) reversal in the terlipressin group (the primary efficacy endpoint), no survival benefit was seen at day 90 compared to the placebo group. By day 90, death occurred in 101 patients (51%) in the terlipressin group and in 45 patients (45%) in the placebo group. Out of the deaths reported within 90 days, 11% of patients in the terlipressin group died due to respiratory disorders compared to 2% of the patients in the placebo group. Furthermore, the incidences of respiratory failure and acute respiratory failure were higher in the terlipressin group than in the placebo group (10% vs. 3% for respiratory failure and 4% vs. 2% for acute respiratory failure). An imbalance in sepsis/septic shock serious adverse events (SAEs) was also observed (7% vs 0%).

Post hoc analysis of the CONFIRM trial showed a worsened outcome in the terlipressin arm compared to the placebo arm in the subgroup of patients with baseline serum creatinine level above 5 mg/dL. A further investigation of patient groups and risk factors associated with an increased risk of respiratory failure and death was therefore warranted.

Administration of albumin to induce and maintain normovolaemia concomitant with terlipressin administration is recommended in cirrhotic patients with initial acute kidney injury (AKI) stadium >1a, according to the European Association for the Study of the Liver (EASL) guideline for the management of patients with decompensated cirrhosis (EASL, 2018). Albumin was accordingly used as standard-of-care treatment in the CONFIRM trial in both study arms. From the results of the CONFIRM trial, a hypothesis has been raised that the observed high incidence of respiratory dysfunction could be due to a potential pharmacodynamic interaction between albumin and terlipressin. The benefit-risk balance of the combined use of albumin and terlipressin therefore required further investigation.

The EU product information recommends bolus administration of terlipressin, and bolus administration was also used in the CONFIRM trial. A study by Cavallin et al. (2016) suggested that continuous infusion of terlipressin is associated with a better safety profile than bolus administration, thereby avoiding high peak plasma concentrations of terlipressin, and hence a possible reduction of serious adverse events including volume overload and respiratory failure. Further investigation of the evidence was warranted to clarify whether the benefit-risk balance of terlipressin in the HRS indication could be improved through an update of the recommended posology.

In the context of the above PSUSA, the PRAC considered that a thorough review in the appropriate procedure is needed for the assessment of the benefit-risk balance of terlipressin in HRS.

On 22 December 2021, in view of the above concerns, the Danish Medicines Agency therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of medicinal products containing terlipressin and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure was limited to the type 1 HRS indication.

2. Scientific discussion

2.1. Introduction

2.1.1. Terlipressin

Terlipressin belongs to the pharmacotherapeutic group "vasopressin and analogues" (ATC H01BA04). Terlipressin is a synthetic analogue of the nonapeptide vasopressin, an endogenous hormone, which has constrictive effects on vascular smooth muscle, inducing splanchnic arteriolar vasoconstriction hence decreased portal tributary inflow with resultant reduction in portal pressure.

In the European Union (EU), terlipressin is indicated for treatment of bleeding oesophageal varices, bleeding in connection with surgery particularly from gastrointestinal and urogenital tracts, and for treatment of hepatorenal syndrome (HRS), specially for type 1 HRS.

Terlipressin is authorised in a total of 26 EU Member States, out of which type 1 HRS is an approved indication in 16 of the Member States. Terlipressin is available as solution for injection and powder for solution for injection. Both formulations are authorized to be administered via intravenous (IV) administration. The recommended posology differs between the indications and Member States, both regarding dosing and the duration of treatment. For type 1 HRS, terlipressin is usually started at a dose of 1 mg of terlipressin acetate every 4-6 hours. The dose can be increased to a maximum of 12 mg daily, or 2 mg every 4-6 hours, if serum creatinine (sCR) levels has not decreased by at least 25% after 2 days of treatment. Treatment is maintained until serum creatinine levels has decreased to<133 µmol/l (<1.5 mg/dl). For patients with partial response (i.e. serum creatinine levels does not decrease to <133 µmol/l), or for patients without response (i.e. no reduction of serum creatinine levels), treatment should be discontinued within 14 days. Standard average duration of treatment is 10 days.

Hepatorenal syndrome can be divided into two types: type 1 and type 2. The type 1 HRS is a life-threatening complication of decompensated cirrhosis with poor prognosis and very limited treatment options. Untreated type 1 HRS is linked to a mortality level of approximately 80% at two weeks, with only 10% of patients surviving more than three months (Alessandria, 2005). In the CONFIRM trial (Wong, 2021), 55% of placebo-treated patients lived for 90 days, which could imply that standard of care treatment for these patients has improved over time. Liver transplantation is the best option for patients but is not always possible due to the short survival expectancy together with transplant availability. From the perspective of the patients, survival is the most relevant effect of an intervention to increase the window of opportunity of a liver transplant.

Albumin and vasoconstrictor therapy are the mainstays of pharmacologic treatment for type 1 HRS. Among the vasoconstrictor therapy, terlipressin is the recommended treatment for type 1 HRS in internationally recognized treatment guidelines, such as those published by the EASL (EASL, 2018) and International Club of Ascites (ICA) [Angeli, 2015]. The EASL recommends the use of terlipressin plus albumin as the first line therapeutic option for the treatment of type 1 HRS. Albumin is used prior to and during terlipressin treatment in most clinical trials and is recommended in combination with terlipressin because of its volume expanding effect, thereby improving effective arterial blood volume. It may also limit the extent of inflammation that accompanies acute decompensated cirrhosis.

To note, the definitions of HRS subtypes were updated in 2015. Type 1 HRS and type 2 HRS were renamed HRS-AKI (hepatorenal syndrome with acute kidney injury) and HRS–NAKI (hepatorenal syndrome with non-acute kidney injury), respectively. The diagnosis of both types was historically based on an increase in sCr of 50% from baseline to a final value >1.5 mg/dl (133 µmol/L) defined

based on time frame sCr increase, but today the definition has changed to reflect whether renal dysfunction is acute, subacute, or chronic (EASL 2018).

2.2. Clinical Data

2.2.1. CONFIRM study

In 2021, new emerging data from the CONFIRM trial was published (Wong, 2021), a prospective, multi-center, randomized, double-blinded, placebo-controlled phase 3 study on the efficacy and safety of terlipressin plus albumin in 300 adults with type 1 HRS randomized in a 2:1 ratio (199 assigned to terlipressin and 101 assigned to placebo). CONFIRM is the largest and most robust study of terlipressin in type 1 HRS patients to date. The study was sponsored by the company Mallinckrodt Pharmaceuticals and used as grounds to seek Food and Drug Administration (FDA) approval for a medicinal product containing terlipressin in the United States of America (USA). The trial was sponsored by this company with the intention of being a confirmatory trial of the efficacy and safety of terlipressin. In addition to the CONFIRM trial, two smaller trials were also included in the terlipressin clinical development programme which formed the regulatory basis for the application to the FDA: OT-0401 (Sanyal, 2008) and the REVERSE trial (Boyer, 2016). 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.

Eligible patients in the CONFIRM trial had a sCr level between 2.25 mg/dL and 7.0 mg/dL prior to randomization. Patients received terlipressin or placebo in a blinded manner for up to 14 days; 1 mg of terlipressin or placebo was administered intravenously as a bolus injection over 2 minutes every 5.5 to 6.5 hours. As per standard medical practice, concomitant use of albumin in both treatment arms was strongly recommended, if clinically appropriate. The primary endpoint was a multi-component endpoint "verified reversal of HRS," defined as two consecutive sCr measurements of 1.5 mg/dl or less at least 2 hours apart and survival without renal-replacement therapy for at least 10 days after the completion of treatment. Four prespecified secondary efficacy endpoints were analysed: HRS reversal, defined as a serum creatinine level of 1.5 mg/dL or less; durability of HRS reversal, defined as HRS reversal without renal-replacement therapy to day 30; HRS reversal among patients with systemic inflammatory response syndrome; and verified reversal of HRS without recurrence of HRS by day 30. Data on non-SAEs were collected up to 7 days after the end of the treatment period, and data on SAEs were collected up to 30 days after the end of the treatment period. Mortality was documented for up to 90 days after the first dose of terlipressin or placebo.

2.2.2. Data on safety

The PRAC considered all available data in relation to the safety concerns highlighted, including clinical data (CONFIRM trial and pooled data for 3 trials [OT-0401, REVERSE, CONFIRM][1]), data from the literature and from spontaneous reporting provided by the MAHs. A summary of the most relevant information is included below.

[1] The pooled data (simple pooling) from these studies were used as supportive safety data in FDA's evaluation. These data are referred to as the Integrated Summary of Safety, ISS.

2.2.2.1. Mortality

CONFIRM trial and integrated summary of safety (ISS) data

In the CONFIRM trial, mortality up to Day 90 was greater in the terlipressin as compared to the placebo arm (51% vs 44%; 95% confidence interval [CI], −6 to 18). As expected in this patient population, fatal adverse events (AEs) categorized as "hepatic disorders" were the most common cause of death in both arms and were reported at a slightly higher incidence in the placebo as compared to the terlipressin arm. In contrast, fatal AEs associated with respiratory failure, sepsis and septic shock were reported in a higher percentage of subjects in the terlipressin arm in the CONFIRM study; analyses of the pooled study data revealed similar findings.

Death within 90 days due to respiratory disorders occurred in 22 patients (11%) in the terlipressin group and 2 patients (2%) in the placebo group. In the CONFIRM study, the incidence of deaths during the treatment period (treatment-emergent deaths) was higher in the terlipressin arm as compared to the placebo arm (4.5% vs. 1.0%); however, this finding was not seen in the ISS population. The most commonly reported AE leading to death during the treatment period was respiratory failure, which occurred in 6 of the 9 subjects who died in the terlipressin arm (Table 1).

Table 1 - Deaths up to Day 90 in Safety Population, CONFIRM Study and ISS

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

Source: Reviewer's analysis, dataset: ISS adsl & adae
[1] Defined as death occurred up to 90 days from start of the treatment. Subjects could have more than one AE leading to a fatal outcome. This table only lists the most common fatal events
[2] Defined as Standardised MedDRA Query (narrow)
[3] Treatment-emergent defined as death occurred on same day as when last dose of study was administrated
Abbreviations: N, number of subjects in group; n, number of deaths; ISS, integrated summary of safety

Source: FDA Briefing Document, 2020 (Table 22)

Table 2 presents the timing of death up to Day 90 observed both in the CONFIRM study and ISS. Approximately 50% of deaths in both arms occurred by Day 14. A large proportion of subjects died by the 30-day follow-up visit (38% on terlipressin and 35% on placebo), which is not unexpected given the patient population. The majority of subjects who did not receive a transplant either initiated renal replacement therapy (RRT) or died by Day 90. The proportion of subjects who initiated RRT or died during this time period was similar between the two arms (73% terlipressin versus 74% placebo). By Day 90, a slightly lower proportion of subjects on terlipressin compared to placebo had received a liver transplant (23% of all the subjects in the terlipressin arm versus 29% of all the subjects in the placebo arm, regardless of baseline transplant status). Twenty-five percent of subjects on terlipressin who were listed for a transplant at baseline did not receive a liver transplant by Day 90 and died, compared to none in the placebo arm. The K-M curves of deaths up to Day 90 show that the incidence of death was similar between the two arms through Day 40 and separated beyond that (Figure 1).

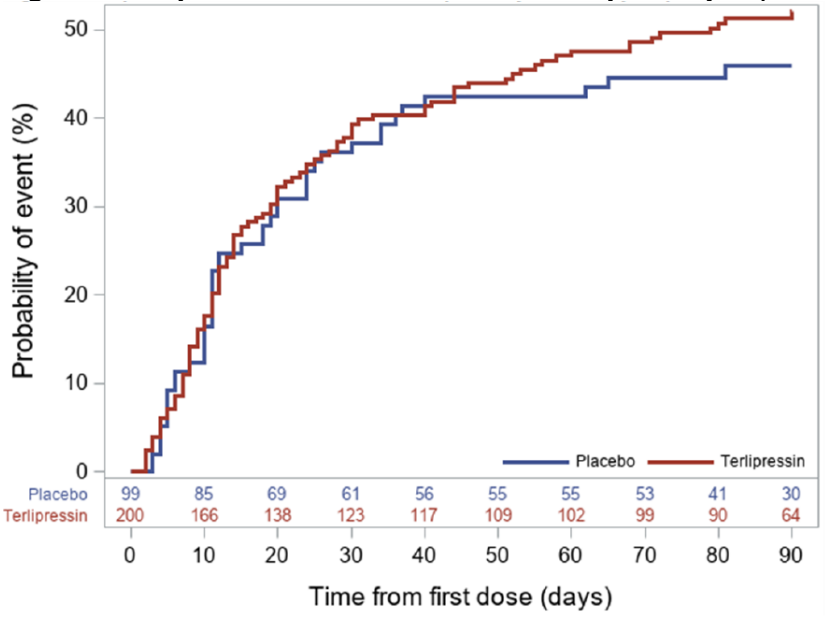
Table 2 - Timing of death up to Day 90, safety population, CONFIRM Study and ISS

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

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

Source: FDA Briefing Document, 2020 (Table 23)

Figure 1 - Kaplan-Meier estimates of death up to Day 90, safety population, CONFIRM study



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

Source: FDA Briefing Document, 2020 (Figure 7)

Subgroup analysis/ Risk factors

Serum creatinine (sCR) level

The pooled data from the 3 trials (OT-0401, REVERSE, CONFIRM) indicated that in patients with baseline sCr above 5.0 mg/dl, terlipressin is associated with 2-fold increased risk of death compared to placebo after 14 days (Table 3). In absolute measures, it is a 27.2% difference in mortality favouring placebo treatment, and therefore it is plausible that patients with baseline sCr levels above 5 mg/dl do not benefit from treatment with terlipressin. Across the 3 studies, 77 patients out of 608 patients (12.7% of the study population) had baseline sCR ≥ 5.0 mg/dl.

Table 3 - Mortality with baseline sCr ≥ 5 mg/dl and < 5 mg/dl

	Baseline SCr ≥5 mg/dL		Baseline SCr <5 mg/dL	
	Terlipressin N=44 %	Placebo N=33 %	Terlipressin N=308 %	Placebo N=223 %
Death by Day 14	54.5	27.3	20.8	23.3
Death by Day 90	70.5	51.5	45.1	47.5

Source: Mallinckrodt Pharmaceuticals, NDA 22-231, Terlipressin for the Treatment of HRS Type 1, Presentation for the Cardiovascular and Renal Drugs Advisory Committee, 2020 (CC-102)

When assessed by baseline SCr, the incidence of severe and serious AEs and AEs 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 multiorgan 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).

Acute-on-chronic liver failure (ACLF) grade

When assessed by baseline acute-on-chronic liver failure (ACLF) grade, the data from the integrated studies (OT-0401, REVERSE, CONFIRM) showed that patients with ACLF score 3 treated with terlipressin had a higher mortality. Death by Day 90 was observed in 66.7% of the patients with ACLF grade 3 treated with terlipressin compared to 53.1% of the patients with ACLF grade 3 in the placebo group. In patients with baseline ACLF 0-2, mortality was higher in the placebo group (Figure 2).

Figure 2 - Mortality with baseline ACLF 0-2 and 3

Mortality With Baseline ACLF 0-2 and 3
Integrated Studies (ITT Population)

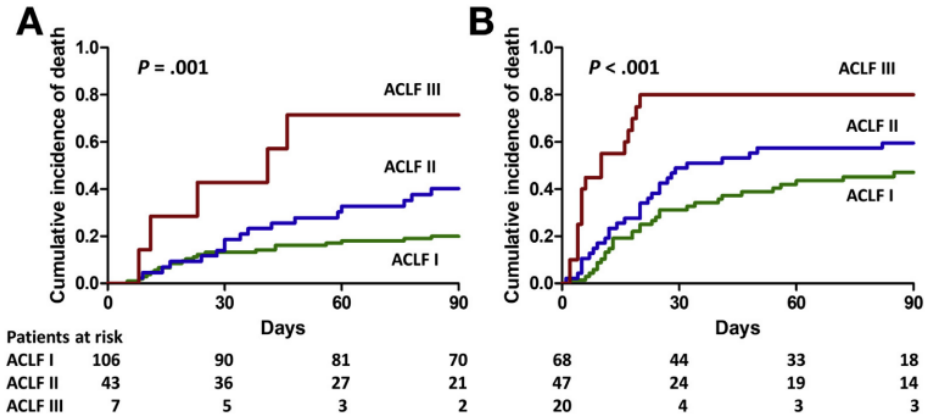
	Baseline ACLF 3		Baseline ACLF 0-2	
	Terlipressin N=72 %	Placebo N=49 %	Terlipressin N=280 %	Placebo N=206 %
Death by Day 14	47.2	38.8	19.3	20.4
Death by Day 90	66.7	53.1	43.6	46.6

Source: Mallinckrodt Pharmaceuticals, NDA 22-231, Terlipressin for the Treatment of HRS Type 1, Presentation for the Cardiovascular and Renal Drugs Advisory Committee (CC-101)

Piano et al. (2018) performed a retrospective analysis of 4 different cohorts of consecutive patients with HRS treated with terlipressin and albumin from February 2007 through January 2016 in the EU. The studies OT-0401, REVERSE and CONFIRM were not included in this analysis. Of the patients with ACLF grade 1, 60% responded to treatment; among those with ACLF grade 2, 48% responded, and among those with ACLF grade 3, 29% responded (P < 0.001 for comparison between grades). In multivariate analysis, baseline ACLF grade (odds ratio, 0.63; P [0.01]) was independently associated

with response to treatment. In univariate analysis, response to treatment was also a main determinant of survival. Indeed, the cumulative incidence of mortality was significantly lower in responders than in non-responders (28 vs 57%; P < 0.001). More in detail, in patients with ACLF grade 1 and 2, responders had a significant decrease in 90-day mortality than non-responders (20% vs 47%, P < .001; 40 vs 60%, P < 0.018; for grade 1 and 2, respectively), while no difference was observed in patients with ACLF grade 3 (71% vs 80%; P < 0.201) [Figure 3]. However, a trend towards an improvement in 28-day mortality was observed in responders vs non-responders with ACLF grade 3 (43% vs 80%; P < 0.063). Interestingly, mortality rate increased according to ACLF grade both in responders and non-responders.

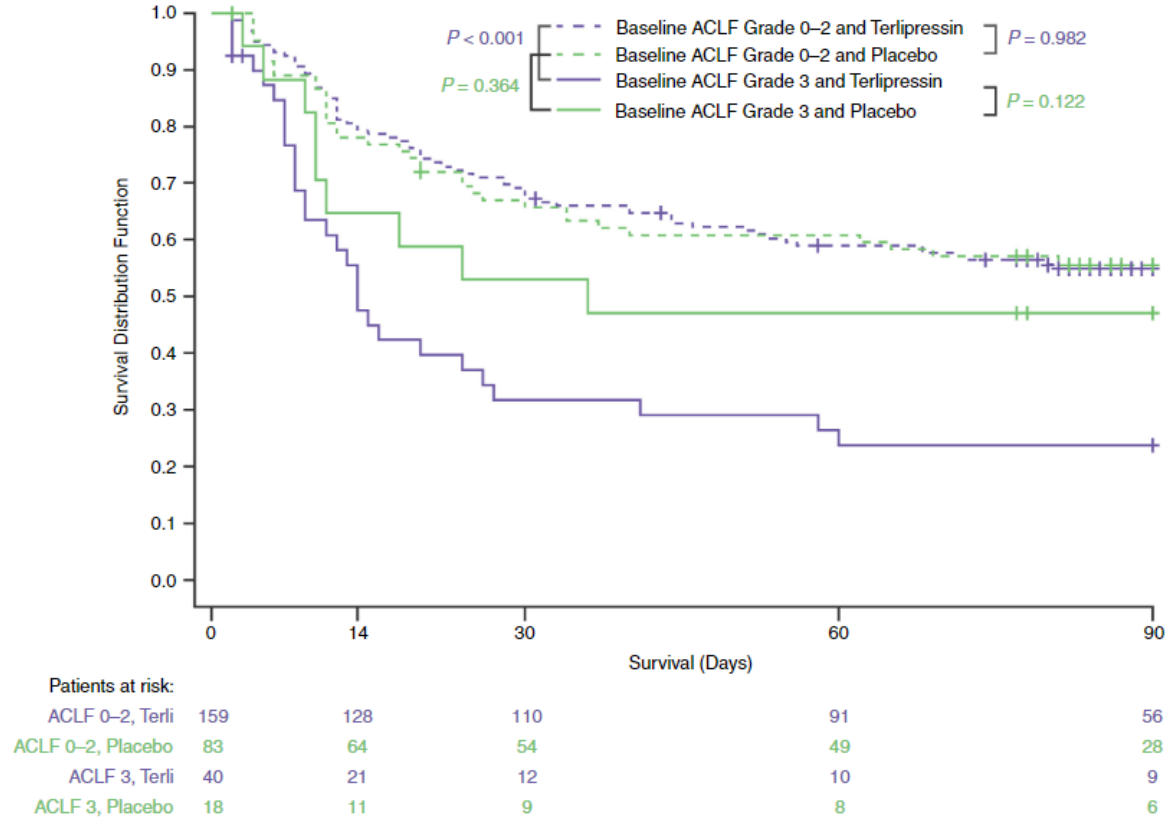
Figure 3 – Cumulative incidence of mortality at 90-day according to ALCF grade in responders (A) and non-responders (B) to treatment with terlipressin and albumin



Source: Piano, 2018

A recently published post hoc analysis of the CONFIRM study by Wong et al. (2022) reported further on the impact of ACLF grade on mortality. Subcategories of ACLF grades were used to assess mortality given that there were increased deaths from respiratory failure in patients with grade 3 ACLF who received terlipressin. There was no difference in mortality between the terlipressin and placebo subgroups in those patients with ACLF grades 1–2. However, in the terlipressin group, mortality was significantly higher in patients with grade 3 ACLF versus those with grades 1–2 ACLF (p < 0.001; Figure 4). Overall survival to 90 days in patients with baseline ACLF grade 1a (kidney failure-HRS only) was similar in the terlipressin and placebo groups, p = 0.7183. Competing risk analysis indicated that in patients with baseline ACLF grade 3, there was a significant difference in the cumulative incidence function for the competing events of transplant or death for terlipressin compared to placebo (Gray's p= 0.039); for patients with ACLF < grade 3, there was no significant impact of treatment on CIF estimates for those competing events (Gray's p = 0.780).

Figure 4 – Mortality in patients up to 90 days by treatment group and baseline ACLF grade (safety population)



Source: Wong, 2022

2.2.2.2. Respiratory Events and fluid overload

Based on its pharmacodynamic activity, terlipressin is known to have cardiovascular and pulmonary effects that include increased mean arterial pressure (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 vasopressin 1 (V1) receptor-mediated constrictor of smooth muscle and, while the presence of V1 receptors in bronchial muscle has not been demonstrated, V1 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 (Mallinckrodt Pharmaceuticals Briefing document, 2020).

Patients with decompensated cirrhosis and type 1 HRS 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 gastrointestinal bleeding.

Acute respiratory failure is linked to mortality in patients with end-stage liver disease. These patients may develop acute respiratory failure for reasons specific to advanced liver disease, including hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax. They may also develop respiratory complications due to conditions seen in the general intensive care unit (ICU) population to which ESLD patients are at higher risk, including infection, volume overload, and the

acute respiratory distress syndrome (Wang 2018). Furthermore, hypoalbuminemia, which is highly common in patients with decompensated cirrhosis, can lead to pulmonary oedema. Also, hyponatremia can be associated with respiratory failure.

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, 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. In this setting, the vasoactive effects of terlipressin may exacerbate perturbations of perfusion/ventilation relationships in the lung.

CONFIRM trial and integrated summary of safety (ISS) data

Respiratory events

The results from the CONFIRM trial seem to point that terlipressin adds further to the existing risk level of respiratory failure in the patient population. The incidence of respiratory-related AEs (events in the respiratory, thoracic, and mediastinal disorder system organ class) was higher in the terlipressin arm (40%) than in the placebo arm (25%). Death within 90 days due to respiratory disorders occurred in 22 patients (11%) in the terlipressin group and 2 patients (2%) in the placebo group. The most commonly reported respiratory AEs in the terlipressin arm were respiratory failure, dyspnoea, pulmonary oedema and pleural effusion and these events were reported at a higher incidence in the terlipressin than in the placebo arm (Table 4).

Most of the respiratory AEs occurred within 10 days after the first dose of study treatment with a median onset of 3 to 4 days. While most of the respiratory AEs were reported to be mild to moderate in intensity, about 90% of respiratory failure events and about 30% of pulmonary oedema events were reported to be severe.

Table 4 - Incidence of respiratory AEs, safety population, CONFIRM Study and ISS

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

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

Source: FDA Briefing Document, 2020 (Table 28)

A higher incidence of respiratory failure SAEs was reported in the terlipressin arm as compared to the placebo arm [14% versus 5.1%, RD=8.9 (2.4, 15.4)] in the CONFIRM study. Sixty percent of these

events (17/28, 61%) in the terlipressin arm resulted in death, while one fatal respiratory failure event was reported in the placebo arm (1/5, 20%) (Table 5).

Table 5 - Incidence and severity of respiratory failure AEs and SAEs across studies

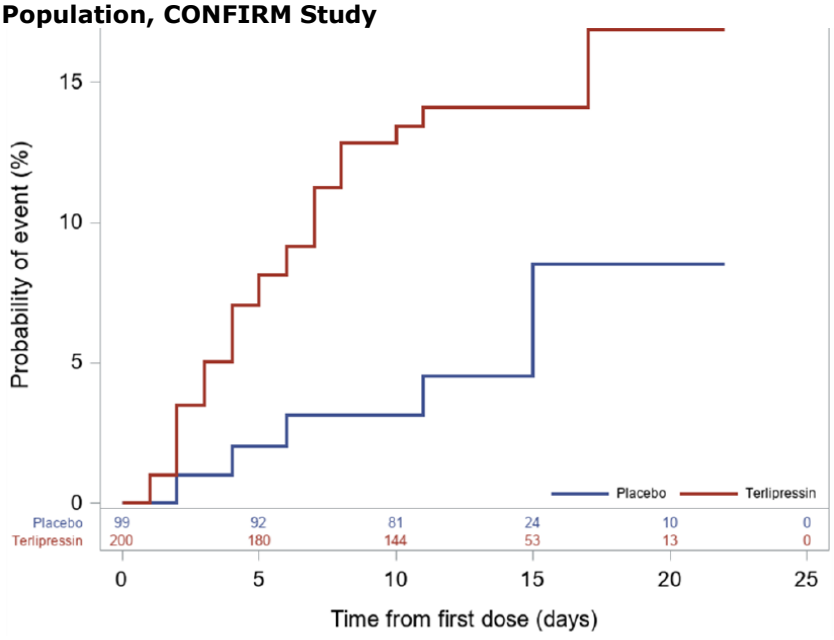
	OT-0401		REVERSE		CONFIRM	
	Placebo (N=55)	Terlipressin (N=56)	Placebo (N=95)	Terlipressin (N=93)	Placebo (N=99)	Terlipressin (N=200)
Respiratory failure AEs	5 (9.1)	6 (10.7)	10 (10.5)	16 (17.2)	10 (10.1)	36 (18.0)
Severe	4 (7.3)	5 (8.9)	7 (7.4)	9 (9.7)	6 (6.1)	32 (16.0)
Moderate	0	1 (1.8)	2 (2.1)	5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

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

Source: FDA Briefing Document, 2020 (Table 29)

The majority of these serious respiratory failure events in the terlipressin arm occurred within 10 days with a median onset of 4.5 days (interquartile range [IQR]: 2 to 7 days). Two events occurred on the day the first dose of terlipressin was administered. The Kaplan-Meier (K-M) curves of respiratory SAEs demonstrated an early separation between the arms (Figure 5). The early occurrence of respiratory AEs support that it is related to treatment rather than e.g. selection bias between groups.

Figure 5 - Kaplan-Meier estimates of respiratory failure serious adverse events, safety Population, CONFIRM Study



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

Source: FDA Briefing Document, 2020 (Figure 8)

From the pooled dataset, the incidence of respiratory failure caused by terlipressin was markedly higher than the estimated incidence according to the approved SmPC section 4.8 in EU, where respiratory failure is currently listed with frequency uncommon. The incidence and severity of respiratory failure AEs increased over time in the terlipressin arm across the three studies (CONFIRM > REVERSE > OT-0401): no signal for respiratory failure was evident in the first study (OT-0401); in the second study (REVERSE), there was a trend towards a greater frequency of respiratory failure AEs in the terlipressin arm, but no trend for SAEs; in the CONFIRM study, trends were evident in both SAEs and all AEs; the same trend was not observed in the placebo arm.

Hemodynamic oedema, effusions and fluid overload

An analysis of Standardised MedDRA Queries (SMQs) revealed a higher incidence of AEs in the terlipressin arm as compared to the placebo arm for the SMQ of "hemodynamic edema, effusions and fluid overload" in the CONFIRM study (Table 6). The majority of these AEs were reported to be mild to moderate in severity; however about 40% of these events in the terlipressin arm did not recover/resolve during the follow-up period. The most concerning fluid overload AE was pulmonary oedema. More than 80% of pulmonary oedema AEs in the terlipressin arm in the CONFIRM study were of moderate to severe intensity; one was reported as having a fatal outcome. All pulmonary oedema AEs in the terlipressin arm occurred within 7 days of initiating study drug with a median onset of 4 days (IQR: 3 to 4 days).

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

Table 6- Incidence and severity of fluid overload related adverse events across studies

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

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

Source: FDA Briefing Document, 2020 (Table 30)

Literature data

Fluid overload SAEs have been demonstrated in other terlipressin use studies. In the OT-0401 study (Sanyal, 2008), the incidence of SAEs related to study treatment was 9% in participants treated with terlipressin and albumin versus 2% in participants treated with placebo and albumin. Similar to CONFIRM, 40% of terlipressin–treated patients with SAEs had respiratory distress. In the study by Martin Llahi et al (2008), 2 out of 23 patients in the terlipressin+albumin arm developed respiratory failure of unknown cause, compared to 0 out of 23 cases in the albumin arm. In this study, the incidence of "circulatory overload" was of 30% in the terlipressin and albumin arm as compared with 17% in the placebo and albumin arm (P=0.87). The United Kingdom (UK) real-world evidence study (Moore, 2020) also shows a high observed proportion of fluid overload/pulmonary oedema events (16%) in type 1 HRS patients in a European setting.

Spontaneous reports

At start of the referral procedure, MAHs were requested to present a cumulative review of all cases of 'Haemodynamic oedema, effusions and fluid overload' (SMQ, broad) and 'respiratory failure' (SMQ, broad) with information about prior and concomitant albumin use and other risk factors for each case, if possible. Cumulatively up to 14 January 2022, the MAH Ferring reported a total of 67 events within the SMQ 'Haemodynamic oedema, effusions and fluid overload' (broad) and 'Respiratory failure' (broad), captured in 62 cases. 62 events were assessed as serious and 5 events as non-serious. Forty-three (43) cases were spontaneous or originated from literature, and 19 originated from Ferring or non-Ferring studies. Forty-four (44) cases were considered related and 18 cases non-related by the MAH.

Based on the cumulative review of cases of respiratory disorders, haemodynamic oedema, effusions and fluid overload presented by the MAH, no firm conclusion could be drawn. Given the medical complexities and multiple potential causes of these events in type 1 HRS patients, it is challenging to determine the role of terlipressin and other risk factor, including the concomitant albumin use may have played in individual cases. Therefore, it was concluded that the evaluation of these safety concerns should mainly be based on evidence from randomised clinical trials.

Subgroup analysis/ Risk factors

Patients with severe reduction in liver function (ACLF grade and MELD score)

According to post hoc subgroup analysis of the CONFIRM study, the group of patients with severe reduction in liver function, in particular patients with ACLF grade 3 and MELD score ≥39, had the highest risk difference for developing respiratory failure (Table 7, Table 8 and Figure 6) and fluid overload-related SAEs when treated with terlipressin compared to placebo. The risk of developing respiratory failure SAEs was also higher in older patients (age ≥55 years old). The mechanism between severely reduced liver function and increased sensitivity to terlipressin-induced respiratory disorders is not at present clear, and the association could be confounded by other factors.

Table 7 - Selected SAEs by ACLF grade (≥5% incidence in terlipressin ACLF grade 3 group); CONFIRM study (safety population)

	Baseline ACLF Grade 0-2		Baseline ACLF Grade 3	
	Terlipressin N=160 %	Placebo N=81 %	Terlipressin N=40 %	Placebo N=18 %
Overall	61.3	59.3	80.0	66.7
Respiratory failure	6.3	3.7	25.0	0
Multiple organ dysfunction syndrome	3.1	2.5	10.0	5.6
Abdominal pain	4.4	1.2	7.5	0
Hepatic failure	3.8	6.2	7.5	27.8
Sepsis	3.8	0	7.5	0
Gastrointestinal hemorrhage	3.1	0	7.5	0
Hepatic cirrhosis	1.9	2.5	7.5	0
Chronic hepatic failure	4.4	8.6	5.0	5.6
Acute respiratory failure	3.8	2.5	5.0	0
Shock	1.9	2.5	5.0	5.6
Cirrhosis alcoholic	1.3	1.2	5.0	11.1

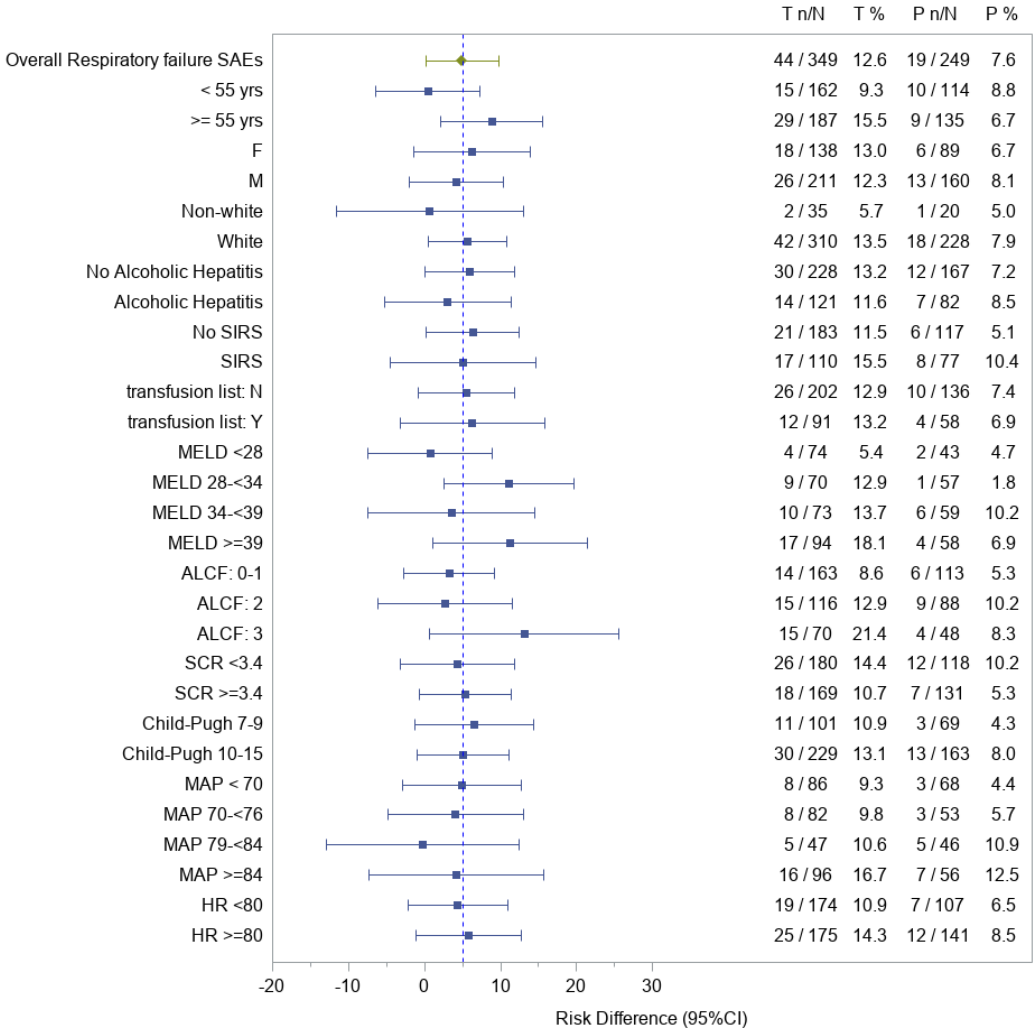
Source: Mallinckrodt Pharmaceuticals, NDA 22-231, Terlipressin for the Treatment of HRS Type 1, Presentation for the Cardiovascular and Renal Drugs Advisory Committee (BU-696)

Table 8 – Selected AEs leading to death by ACLF grade (≥5% Incidence in Terlipressin ACLF grade 3 group); CONFIRM study (safety population)

	Baseline ACLF Grade 0-2		Baseline ACLF Grade 3	
	Terlipressin N=160 %	Placebo N=81 %	Terlipressin N=40 %	Placebo N=18 %
Overall	45.6	43.2	72.5	50.0
Respiratory failure	3.1	0	17.5	0
Multiple organ dysfunction syndrome	4.4	4.9	10.0	5.6
Chronic hepatic failure	6.9	8.6	7.5	5.6
Hepatic failure	5.0	6.2	7.5	22.2
Hepatic cirrhosis	3.1	2.5	7.5	0
Sepsis	1.3	0	7.5	0
Acute respiratory failure	2.5	1.2	5.0	0
Cirrhosis alcoholic	1.9	1.2	5.0	11.1

Source: Mallinckrodt Pharmaceuticals, NDA 22-231, Terlipressin for the Treatment of HRS Type 1, Presentation for the Cardiovascular and Renal Drugs Advisory Committee (BU-695)

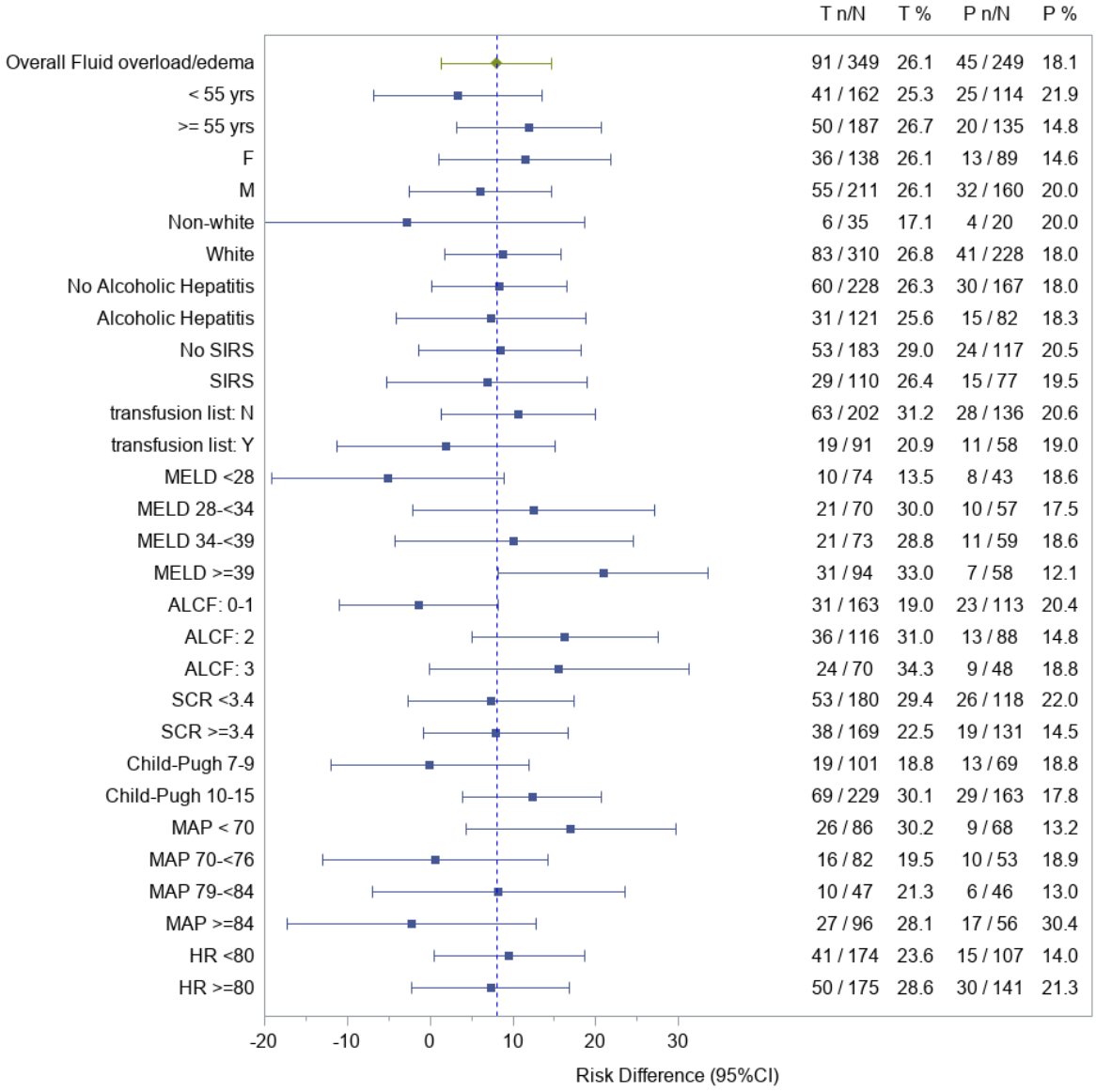
Figure 6 - Subgroup analysis for respiratory failure serious adverse events, safety population, ISS



Source: FDA Briefing Document, 2020 (Figure 9)

Using the ISS data, subgroup analyses of fluid overload-related AEs were performed. Overall, the results were consistent across most of the subgroups with an overall risk difference (RD) of 8.0 (95% CI: 1.4-14.6), favouring placebo. As shown in the Figure 7 below, subgroups that appeared to be at greater risk included those with a Model For End-Stage Liver Disease (MELD) score ≥39 [RD: 20.9 (95% CI: 8.3-33.6)], ACLF Grade 2 and Grade 3 liver failure [RD: 16.3 (95% CI: 5.0-27.5) and 15.5 (95% CI: -0.1-31.2), respectively] and MAP <70 mmHg [RD: 71.0 (95% CI: 4.4-29.6)].

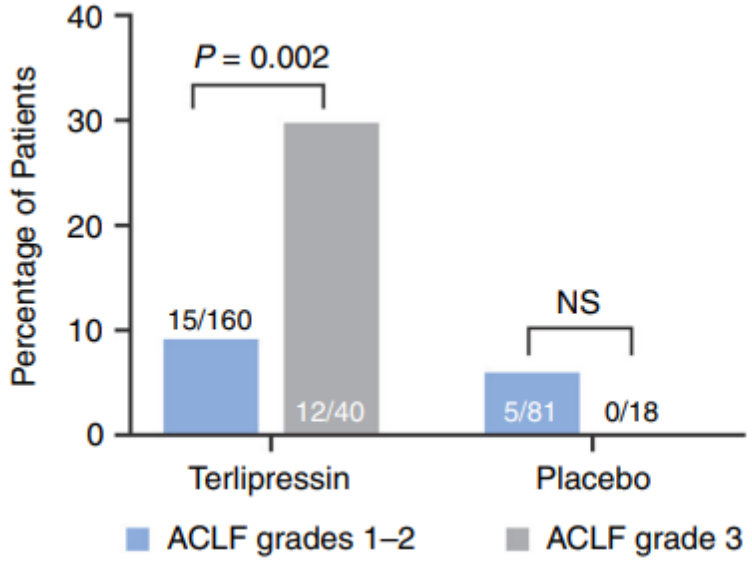
Figure 7 - Subgroup analysis for fluid overload–related AEs, safety population, ISS



Source: FDA Briefing Document, 2020 (Figure 10)

In the recently published post hoc analysis of the CONFIRM study, the impact of ACLF grade on risk of respiratory failure was further reported (Wong, 2022). The incidence of respiratory failure as reported by study investigators up to 30 days post treatment for both study groups, separated by patients with ACLF grades 1–2 versus ACLF grade 3groups, is shown in Figure 8. Within the terlipressin group, a significantly greater number of patients with ACLF grade 3 developed respiratory failure (n = 12/40, 30%) compared with those patients with grades 1–2 ACLF (n = 15/160, 9.4%, p = 0.002). Among those in the ACLF grade 3subgroup, there were significantly more patients who received terlipressin and developed respiratory failure (n = 12/40, 30%), when compared with those who received placebo (n = 0/18, 0%, p = 0.01).

Figure 8 - Percentage of patients with respiratory failure serious adverse events up to 30 days post treatment by treatment group and baseline ACLF grade (safety population)

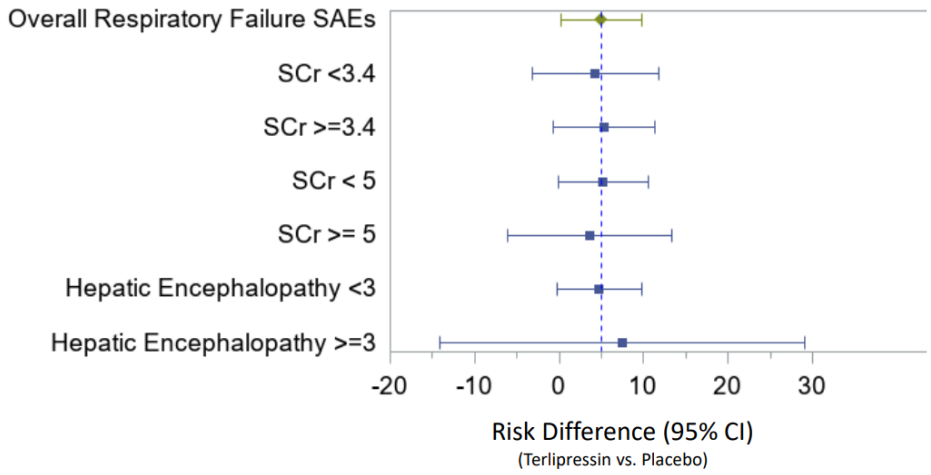


Source: Wong, 2022 (Figure 2B)

Serum creatinine (sCR) level

In an analysis performed by the FDA, there was no difference in respiratory failure SAEs according to baseline sCr < 3.4 mg/dl vs. > 3.4 mg/dl and sCr < 5.0 vs. > 5.0 mg/dL, using ISS data (Figure 9). FDA analysis of this aspect showed no difference in incidence of respiratory SAEs between subgroups of baseline sCr, and in fact the numerical incidence of respiratory failure was higher in patients with sCr < 3.4 mg/dl in both the terlipressin group as well as in the placebo group in the CONFIRM trial, which means the risk of respiratory failure is increased regardless of baseline sCr level.

Figure 9 - Subgroup analysis for overall respiratory failure SAEs



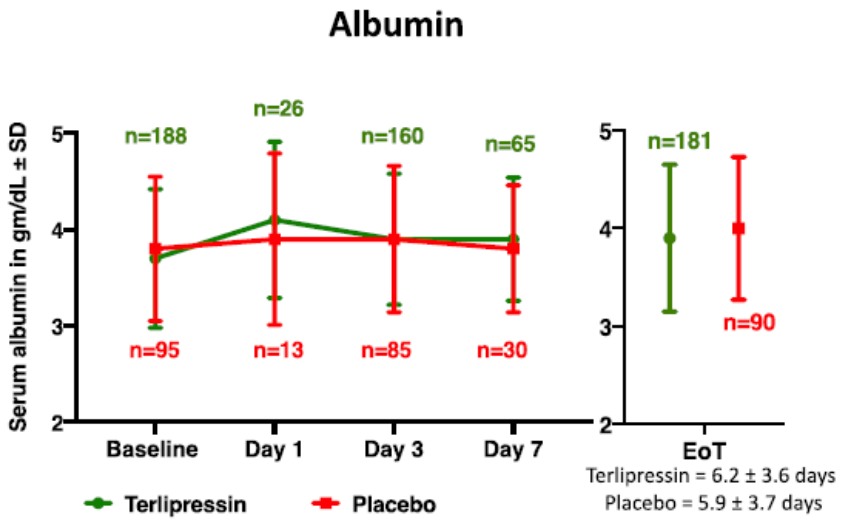
Source: FDA presentation, 2020 (Figure in slide 36)

Albumin use

From the results of the CONFIRM trial, a hypothesis has been raised that the observed high incidence of respiratory dysfunction could be due to a potential pharmacodynamic interaction between albumin

and terlipressin. In the CONFIRM trial, patients started terlipressin treatment at high mean baseline serum albumin levels: 3.7±0.7 g/dl and 4.0±2.6 g/dl in the terlipressin and placebo treatment arm, respectively (Figure 10), as many received albumin during the screening period (14 days). Mean total prior albumin was administered in the terlipressin arm at 335 grams and in the placebo arm 370.7 grams.

Figure 10 - Serum albumin levels for the 2 study groups during the study period (CONFIRM study)



Source: Wong, 2021 (Figure S8)

Analyses using the ISS data showed that the incidence of respiratory failure SAEs increased as prior to baseline albumin use increased in the terlipressin arm; however, a similar trend was not observed in the placebo arm (Table 9). It however has to be also considered, that the increased dosing of albumin might be reflective of the fact that larger doses were used in patients who were overall more unwell, thus also being at more risk to develop respiratory SAEs. Overall, there was a trend for an increased risk of respiratory failure SAEs in the terlipressin arm as compared to the placebo arm among subjects with greater albumin exposure prior to study treatment.

Table 9 - Incidence of respiratory failure SAEs by total prior albumin exposure, ISS

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

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

Source: FDA Briefing Document, 2020 (Table 31)

Comparison of albumin dosages across trials does not point to a specific pattern of concern in regards to the AEs observed.

The potential effectiveness of targeted albumin therapy to reach albumin levels of 30 g/L versus standard of care in patients with decompensated cirrhosis was recently investigated in the ATTIRE trial performed in the United Kingdom (China et al. 2020). The results showed that targeted therapy was not more beneficial than UK-based standard of care but lead to more pulmonary oedema SAEs (15/380 or 3.9% vs 4/397 or 1.0% in the targeted albumin group and in the standard of care group,

respectively). Throughout the trial, a median of 200 g (interquartile range, 140 to 280) of albumin per patient was administered in the albumin group, as compared with 20 g (interquartile range, 0 to 120) administered in the standard-care group (adjusted mean difference, 143 g; 95% confidence interval [CI], 127 to 158.2). A total of 196 of 397 patients (49.4%) in the standard-care group did not receive any albumin. In another study, pulmonary oedema developed in 8/96 (8.3%) patients in the albumin group of whom two died, one on the day and the other on day 33 following albumin infusion (Thevenot, 2015). The study evaluated a total of 193 cirrhotic patients with a Child-Pugh score greater than 8 and sepsis unrelated to SBP were randomly assigned to receive antibiotics plus albumin (1.5 g/kg on day 1 and 1 g/kg on day 3; albumin group: n = 96) or antibiotics alone (control group, n = 97). The primary endpoint was the 3-month renal failure rate (increase in creatinine ⩾50% to reach a final value ⩾133 µmol/L). Outcome after pulmonary oedema was more favourable in the remaining six patients, in whom oedema occurred within the first three days after albumin infusion. These results indicate that high dose albumin therapy alone can lead to increased risk of respiratory adverse events.

Controversially, a recent meta-analysis (Salerno, 2015) including 19 clinical studies showed that the most important factor in predicting a successful response to albumin therapy appears to be the cumulative dose. This meta-analysis observed a dose-response relationship between the amount of infused albumin and survival, with significantly improved survival with increasing 100-gram increments, and expected 30-day survival rates among patients receiving cumulative albumin doses of 200, 400, and 600 g were 43.2%, 51.4%, and 59.0%, respectively, independent of treatment duration, vasoconstrictor type, or mean arterial pressure (Salerno, 2015). The mean cumulative dose of albumin administered was < 200 g in 7 of the patient groups (29.2 %), 200–400 g in 10 (41.6 %) and > 400 g in 7 (29.2 %). The daily albumin dose averaged < 30 g in 10 groups (41.6 %), 30–40 g in 7 (29.2 %) and > 40 g in 7 (29.2 %). The concentration of albumin infused was 20 % in all 10 groups for which specified. Albumin was co-administered with terlipressin in 15 groups (62.5 %), midodrine/octreotide in 5 (20.8 %) and noradrenaline in 4 (16.7 %). The mean duration of albumin/vasoconstrictor therapy was < 8 d in 10 groups (41.7 %), 8–14 d in 9 (37.5 %) and > 14 d in 5 (20.8 %). Data on AEs were not provided in this meta-analysis, and thus the dose-relationship on AEs cannot be discussed.

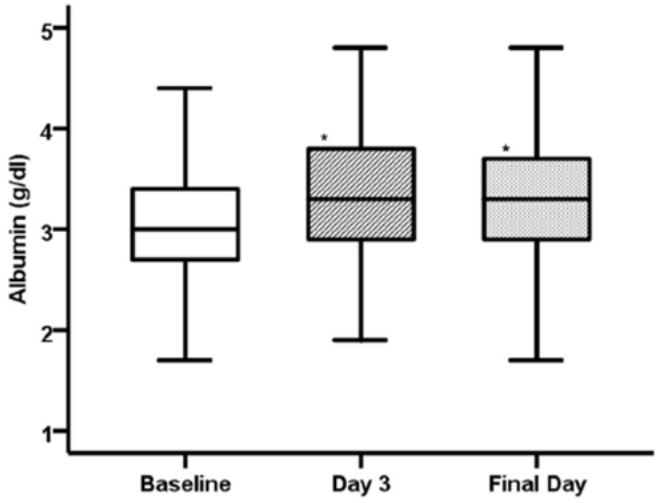
The role of albumin in the development of fluid overload in patients with decompensated cirrhosis was known and was also compensated for according to the CONFIRM study protocol. Thus, the authors theorized fluid overload in patients with decompensated cirrhosis should be initially managed by decreasing the administration of albumin and other fluids and judicious use of diuretics. According to the Mallinckrodt Pharmaceuticals Briefing document, 2020: *"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.".*

It is therefore important to notice that the imbalance in respiratory AEs in the CONFIRM trial occurred despite corrective initiatives of albumin infusion, also that no events of fluid overload apparently preceded a fatal outcome. In this respect, the role of albumin for the event respiratory failure appears unclear.

It was argued during the assessment that the findings from the CONFIRM trial are not relevant for an EU population because the use of albumin is less in Europe compared to the use in the CONFIRM trial and in US in general. Indeed, according to an observational study on patients from across several

European countries collected from 2007 to 2016 (Piano, 2018), serum albumin levels at baseline and day 3 after the albumin loading dose are lower than in the CONFIRM study population (Figure 11).

Figure 11 - Albumin concentration at baseline, at day 3, and end of treatment with terlipressin and albumin.

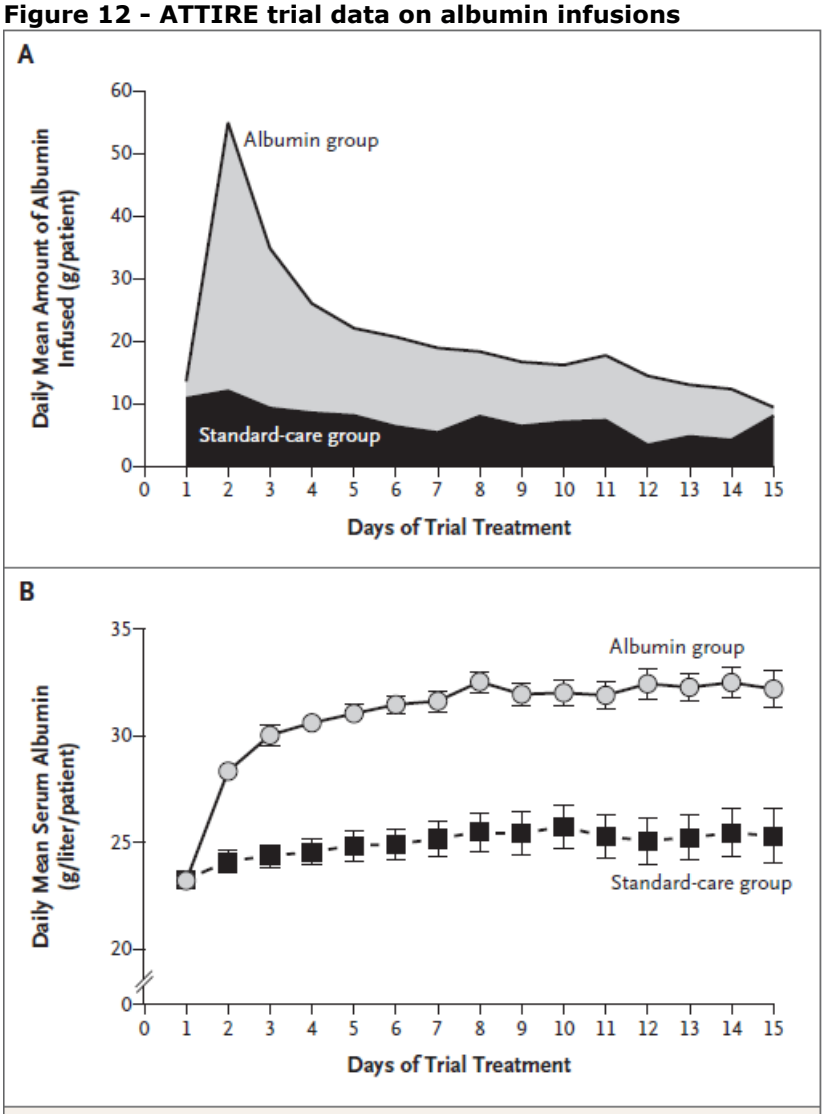


Source: Piano, 2018 (Supplementary Figure 1)
*P < .001 vs baseline.

It has to be considered, that the baseline albumin measurements in the CONFIRM trial were taken after the initial loading doses of albumin had already been given (prior albumin), contrast to other studies, where the baseline has been measured before any albumin given, regardless of this, the baseline measurements still seem high, as explained in the following paragraphs.

According to the below Figure 12 from the ATTIRE paper (China et al. 2020), the ATTIRE Albumin group received a treatment which thereby corresponded well with the EASL recommendation to infuse a dose of 1 g of albumin/kg of body weight for two consecutive days followed by daily doses of 20-40 g per patient.

Figure 12 - ATTIRE trial data on albumin infusions



Source: China, 2021 (Figure 1)

Because it is assumed that EU clinicians adhere to the EASL recommendations, it can be expected that EU type 1 HRS patients will receive albumin treatment corresponding to the targeted albumin treatment regime used in the ATTIRE trial. Indirectly, this would indicate that baseline serum albumin level of around 3.0 g/dl at the time of terlipressin treatment initiation is expected. It is considered, that in light of this information, a mean baseline serum albumin level of 3.7-4.0 g/dl in the CONFIRM trial seems extraordinarily high.

2.2.2.3. Serious Infections

Patients with decompensated cirrhosis and advance ACLF are at high risk for infection. An imbalance in sepsis/septic shock serious adverse events was observed in the CONFIRM trial and the OT-0401 and REVERSE studies. Sepsis/septic shock has not previously been considered an identified risk for terlipressin.

The underlying mechanism could involve an increased risk of bacterial translocation due to intestinal ischaemia. Bacterial translocation is already a well-known complication in decompensated cirrhosis (Tandon 2008), and terlipressin-induced intestinal ischaemia could maybe exacerbate or promote

bacterial translocation and thereby sepsis. It may not be possible to evaluate, but it raises the question of using antibiotics as prophylaxis. There are no trials addressing this issue.

In the CONFIRM study, 14 patients (7%) in the terlipressin arm were reported with SAEs related to sepsis and septic shock vs 0 patients (0%) in the placebo arm; 8/14 of the sepsis patients in the terlipressin arm died due to the event. Sepsis and septic shock SAEs occurred evenly throughout the study with a median onset of 12 days (IQR: 10 to 26 days). The imbalance in sepsis/septic shock SAEs was also observed in the OT-0401 and REVERSE studies. Table 10 presents the pooled safety data from the OT-0401, REVERSE and CONFIRM studies (Mallinckrodt Pharmaceuticals Briefing document, 2020).

Table 10 - 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)

	Integrated Phase 3 Studies	
Preferred Term[a]	**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.

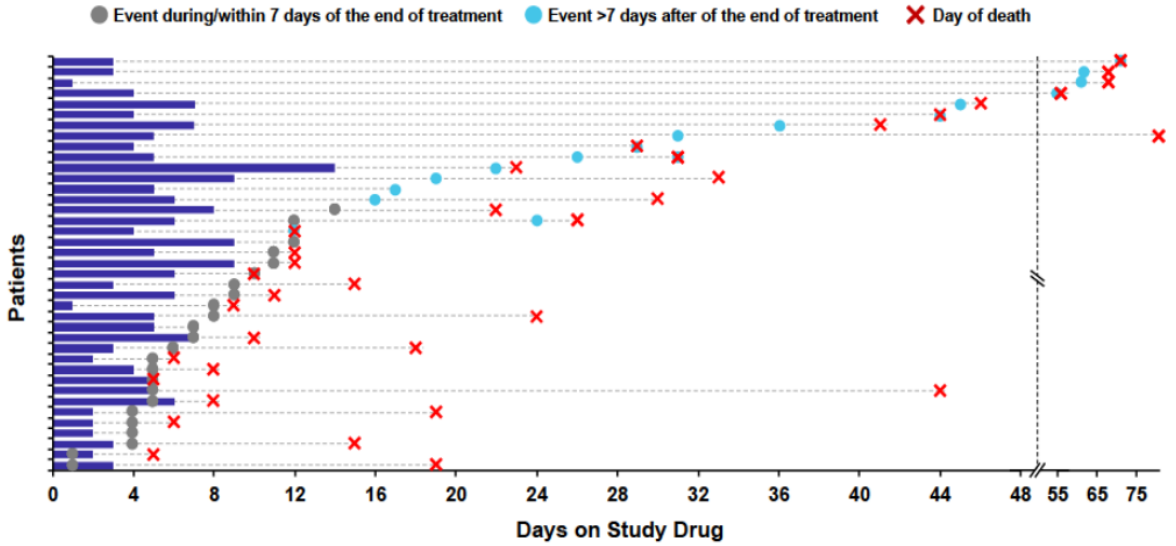
b. Up to 90 days following the start of treatment.

Note: Initial and retreatment periods were combined.

Source: Mallinckrodt Pharmaceuticals Briefing document, 2020 (Table 47)

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 13).

Figure 13 - Subjects with sepsis AEs in the integrated phase 3 terlipressin-treatment group (safety population)



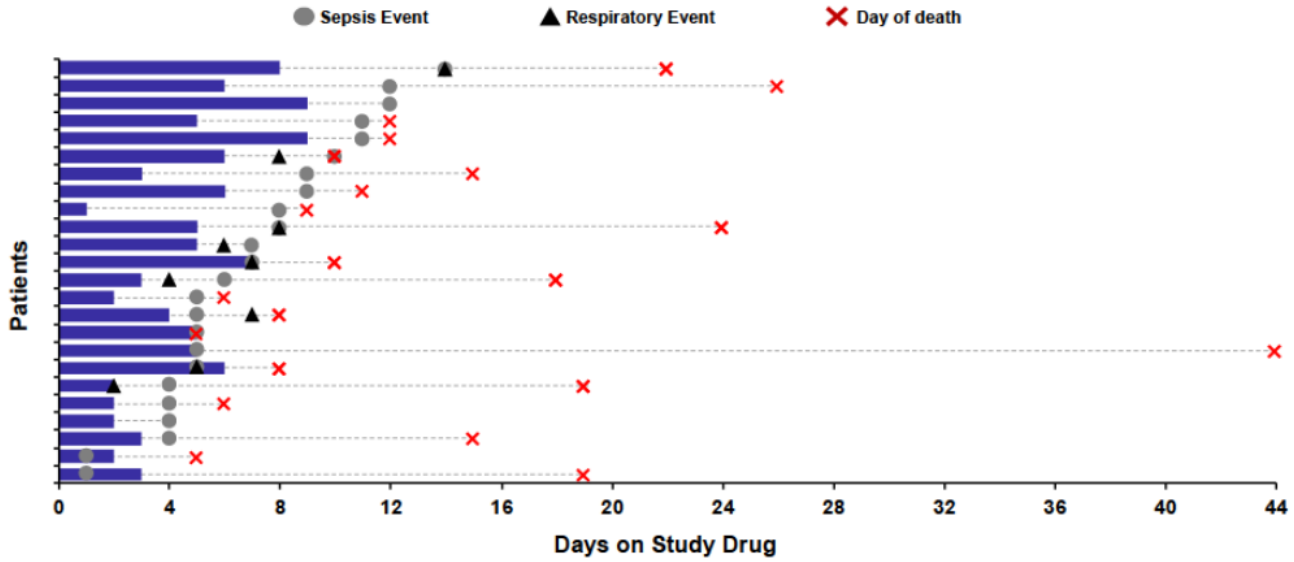
AE, adverse event; N, number of subjects.
The blue bars indicate days on study drug and, for those who died, the red X's indicate date of death. The grey circles represent sepsis events that occurred during or within 7 days of the end of study drug treatment and the blue circles indicate sepsis events 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.

Source: Mallinckrodt Pharmaceuticals Briefing document, 2020 (Figure 28)

Of the 24 terlipressin-treated subjects who experienced sepsis events within 7 days of end of treatment, 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. 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 (Figure 14).

It is theorized, that reducing the risk of respiratory failure, will also impact the frequency of sepsis events (Mallinckrodt Pharmaceuticals Briefing document, 2020).

Figure 14 - 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.

Source: Mallinckrodt Pharmaceuticals Briefing document, 2020 (Figure 29)

The MAH Ferring also conducted a cumulative review of all cases of 'sepsis' (SMQ, broad), which did not provide any new knowledge due to limited information and confounding factors e.g. underlying disease. Cumulatively up to 14 January 2022, Ferring received a total of 19 events within the SMQ 'Sepsis' (broad), captured in 18 cases. All events were assessed as serious. 6 cases were spontaneous or originated from literature, and 12 originated from Ferring or non-Ferring studies. 5 events were considered related by the MAH and 13 events non-related.

Based on the imbalance of sepsis/septic shock cases between the terlipressin arm and the placebo arm in all 3 above-mentioned trials, the fact that the RD of 7% (95% CI = 3.5, 10.5) in the CONFIRM trial is statistically significant (FDA Briefing Document, 2020) and that sepsis/septic shock is a serious event and a potential fatal complication for these patients (60% of the patients with sepsis in the CONFIRM trial died of the event), sepsis is considered an important identified risk.

2.2.2.4. Method of administration

The EASL guideline (EASL, 2018) recommends continuous infusion of terlipressin since overall this route of administration is associated with a better safety profile and has a more stable lowering effect on portal pressure than bolus administration, based on the studies by Cavallin 2016 and Gerbes 2009. By using continuous intravenous infusion, as opposed to bolus administration, and thereby avoiding high peak plasma concentrations of terlipressin, a possible reduction of serious AEs, including volume overload/respiratory failure, may be obtained.

The MAHs presented information about 8 studies (Angeli, 2006, Angeli, 2008, Arora, 2020, Gerbes, 2009, Cavallin, 2015, Cavallin, 2016, Halimi, 2002, Kulkarni, 2022) investigating the effect of continuous intravenous (IV) terlipressin infusion in type 1 HRS in various settings.

Angeli et al. (2008) compared terlipressin given as IV bolus vs terlipressin given as continuous intravenous infusion in the treatment of type 1 HRS in patients with cirrhosis. As an interim analysis, data when either 37 consecutive patients with cirrhosis and type 1 HRS were included and randomised to receive intravenous boluses of terlipressin (group A) or continuous intravenous infusion of terlipressin (group B) were reported. In both groups, albumin was given. Severe adverse effects to treatment were more frequent in patients of group A than in patients of group B (44.4% vs. 26.3%, p=0.05).

The study of Cavallin et al. 2016 found a large difference in treatment-related SAEs (20.59% vs 43.24% in the continuous vs bolus arm, respectively. The study was an open-label randomised controlled multicentre trial. Seventy-eight patients with type 1 HRS were randomly assigned to receive either continuous intravenous infusion at the initial dose of 2 mg/day or intravenous boluses of terlipressin at the initial dose of 0.5 mg every 4 hours. The primary end point of the study was the safety of treatment defined as the prevalence of treatment-related adverse events between the two groups. Secondary endpoints of the study were response to treatment and 90-day transplant-free survival. Both the total rate of treatment-related AEs as well as severe treatment related AEs were significantly lower in the continuous infusion group than in the bolus group (all AEs 35.29% vs 62.16%, $p < 0.025$ and severe AEs 20.59% vs 43.24% ; $p < 0.05$). Complete response was defined by decrease of serum creatinine (sCr) from baseline to a final value of $\leq$ 133 µmol/ L, partial response by a decrease $\geq$50% of sCr from baseline to a final value >133 µmol/L. The rate of response to terlipressin, including both complete and partial response, was not statistically significantly different between the continuous infusion and bolus groups (76% vs 65%). Numerically, the results however favoured the continuous infusion group. The mean daily effective dose of terlipressin was also lower in the continuous infusion group than in the bolus group (2.23 ± 0.65 vs 3.51 ± 1.77 mg/day; $p < 0.05$). The probability of 90-day transplant-free survival was not significantly different between the continuous infusion group and the bolus group (53% versus 69%) (Cavallin, 2016).

The study is however limited in power to make firm conclusions on the effect of continuous infusion specifically on severe respiratory events. There is a tendency favouring continuous infusion on the adverse event 'circulatory overload', defined in the study as "shortness of breath associated with one of the following symptoms: (1) tachypnoea with rales, (2) dilatation of the jugular veins, (3) a central venous pressure (when available) >18 cm H_2O, or (4) radiological signs of pulmonary oedema." Circulatory overload resulting in a need to withdraw terlipressin occurred in 2 out of 34 patients in the continuous infusion arm and 5 out of 37 patients in the bolus infusion arm (Cavallin, 2016).

Of note, the favourable results of continuous infusion compared to bolus administration are supported also by the clinical experience reported in the ad-hoc expert group (AHEG) consulted in the present review. The AHEG experts described that their clinical experiences support the current dosing recommendations of continuous intravenous infusion in the clinical treatment guidelines (EASL, 2018), as well as the two existing national SmPC updates regarding continuous infusion as alternative to bolus infusion already carried out in Italy and Austria. Overall, despite the limitations in the evidence as outlined, it is considered reasonably justified that continuous infusion of terlipressin improves the overall safety profile to an extent that is clinically significant, while efficacy is not affected.

2.2.3. Discussion on safety

The reviewed data identified an increased risk of respiratory failure and sepsis/septic shock with terlipressin compared to what is described in the product information of the terlipressin-containing medicinal products in the EU.

The severity and incidence of respiratory events observed in the CONFIRM study was of concern. The following frequency estimates are obtained from pooled data of Mallinckrodt trials (OT-0401, REVERSE and CONFIRM):

- Respiratory failure: 40 patients experienced respiratory failure SAEs (including respiratory failure and acute respiratory failure) out of 349 patients in the terlipressin arm (40/349=0,115=11.5%), resulting in the frequency of 'very common'.
- Pulmonary oedema: 29 patients experienced pulmonary oedema AEs out of 349 patients in the terlipressin arm (29/349=0.08=8%), resulting in the frequency of 'common'.
- Respiratory distress: 6 patients experienced respiratory distress SAEs (including acute respiratory distress syndrome and respiratory distress) out of 349 patients in the terlipressin arm (6/349=0.017=1.7%), resulting in the frequency of 'common'.
- Dyspnoea: 42 patients experienced dyspnoea AEs out of 349 patients in the terlipressin arm (42/349=0.12=12%), resulting in the frequency of 'very common'.

Fatal AEs associated with respiratory failure, sepsis and septic shock were reported in a higher percentage for terlipressin, which constitutes a major concern related with these events.

When observing the subgroup analysis assessed, the risk of developing respiratory failure SAEs was higher in subjects with advanced disease, as demonstrated among subjects with baseline MELD ≥39 [RD: 11.2 (95% CI: 1.0-21.3)] and ACLF Grade 3 liver failure [RD: 13.1 (95% CI: 0.7- 25.5)] as well as older patients (age ≥55 years old). Therefore, these risk factors may play a role in development of respiratory SAEs. However, respiratory SAEs occurred in patients with lower risk factors likewise. It is plausible, that terlipressin has a role in the development of respiratory SAEs, regardless of the described risk factors. In addition, not all fatal events in the CONFIRM trial had the presence of these underlying risk factors. Furthermore, there was no difference in respiratory failure SAEs according to baseline sCr < 3.4 mg/dl vs. > 3.4 mg/dl and sCr < 5.0 vs. > 5.0 mg/dL. Therefore, it seems that respiratory failure SAEs are unrelated to the baseline sCr value. With these results, it is considered that restricting terlipressin products to patients with lower sCR levels (< 5.0 mg/dL) would be unlikely to influence the occurrence of respiratory SAEs.

The incidence of severe and SAEs and adverse events leading to death was observed to be 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 subgroup are small, this difference between groups appears to be driven by higher incidences in the terlipressin group of fatal AEs of multiorgan 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).

Based on the available evidence from clinical trials and from the cumulative review of cases of respiratory disorders, uncertainty remains about the possible suggested effect modifying role of albumin on the development of fluid overload and respiratory failure. High dose albumin therapy alone can lead to increased risk of respiratory adverse events (China, 2021), and albumin is therefore suspected to play a modifying role of the terlipressin-respiratory failure association. Hence patients

with high serum albumin levels could be at higher risk of respiratory failure when treated with terlipressin. In the reviewed studies (OT-0401, REVERSE trial and CONFIRM), the protocol recommendations on albumin use were in line with general clinical recommendations. However, the actual use was different than according to what was recommended in the protocols. In the CONFIRM trials, prior albumin was used in larger doses than what is recommended in the EASL guidelines. The actual clinical implication of this finding is not known, as no dose-relationship studies have been conducted in regards to the occurrence of AEs in this population. The consulted experts in the AHEG considered that terlipressin also has an effect (e.g., through shifting volume into the thorax and having vasoconstrictive action of the pulmonary veins) but it would need to be considered that these patients were already at an elevated risk, as this level of volume expansion with albumin is not directly applicable to the EU clinical situation. In addition, it is important to notice that the imbalance in respiratory AEs in the CONFIRM trial occurred despite corrective initiatives of albumin infusion as per protocol, and no events of fluid overload apparently preceded a fatal outcome, based on the results presented by Mallinckrodt (Mallinckrodt Pharmaceuticals Briefing document, 2020). In this respect, the effect-modifying role of albumin for the event respiratory failure appears unclear.

Based on the imbalance of sepsis/septic shock cases between the terlipressin arm and the placebo arm in all 3 above-mentioned trials, the fact that the risk difference (RD) of 7% (95% CI = 3.5, 10.5) in the CONFIRM trial is statistically significant (FDA Briefing Document, 2020) and that sepsis/septic shock is a serious event and a potential fatal complication for these patients (60% of the patients with sepsis in the CONFIRM trial died of the event), sepsis is considered an important identified risk of terlipressin with potential impact on the benefit-risk balance and an update of the product information is considered needed.

The following frequency estimate is obtained from pooled data of Mallinckrodt trials (OT-0401, REVERSE and CONFIRM):

- Sepsis: 27 patients experienced sepsis SAEs (sepsis and septic shock SAEs) out of 349 patients in the terlipressin arm (27/349=0,077=7.7%), resulting in the frequency of 'common'.

Lastly, from a safety perspective, continuous infusion appears to be overall safer than bolus injection, although based on a study with relatively low power (Cavallin, 2016). Documentation does not exist that the observed reduction of overall treatment-related AEs (as predefined by Cavallin et al.) is extrapolatable specifically to SAEs of respiratory disorders and sepsis. Although the EASL Guideline (2018) recommends continuous infusion of terlipressin with the argumentation that continuous infusion as opposed to bolus administration is associated with a better safety profile (based on the study by Cavallin, 2016), bolus administration was used in the CONFIRM trial and recommended in all EU product information of terlipressin. Continuous infusion could be a key risk minimisation meausure to ensure a favourable benefit-risk balance, however the grounds for recommending continuous infusion are based on a small study (Cavallin 2016) and clinical experience (AHEG), and, although the potential for extrapolation seems clinically reasonable, the effects down to the specific SAEs of concern, i.e., respiratory failure and sepsis are not clear. The experts also agreed that the Cavallin trial was underpowered to look for specific side effects. Yet, an updated posology recommendation based on the dosage used by Cavallin et al. 2016 and other research groups could be considered warranted for safety reasons, also from the consideration that clinicians could mistakenly convert the existing bolus posology recommendation directly into continuous infusion (i.e., 1 mg/4-6h would then translate to 5 mg/24 h, which is 2.5-fold higher than the dose used in Cavallin, 2016). This would lead to medication error (overdosing of the patients).

2.3. Data on efficacy

The efficacy data supporting the authorized type 1 HRS indication in EU consists of published data from clinical trials, including retrospective and uncontrolled clinical trials as well as randomised, controlled clinical trials, in addition to meta-analyses of published data.

CONFIRM study adds to the efficacy evidence for terlipressin. The study achieved the primary efficacy endpoint with 58/199 patients in the terlipressin arm (29%) as compared to 16/101 patients in the placebo arm (16%) achieving verified HRS reversal (p=0.012). Secondarily, compared to patients in the placebo arm, more patients in the terlipressin arm experienced HRS reversal while on treatment by Day 14 or discharge (36% vs 17%, p<0.001) and HRS reversal without RRT to day 30 (32% vs 16%, p=0.003). The incidence of HRS reversal while on treatment by Day 14 or discharge in the subgroup of patients with systemic inflammatory response syndrome was also significantly greater in the terlipressin arm as compared to placebo arm (33% vs 6%, p<0.001). The proportion of patients with verified HRS reversal without HRS recurrence by Day 30 was numerically greater in the terlipressin arm, but the difference between groups was not statistically significant (24% vs 16%, p=0.09).

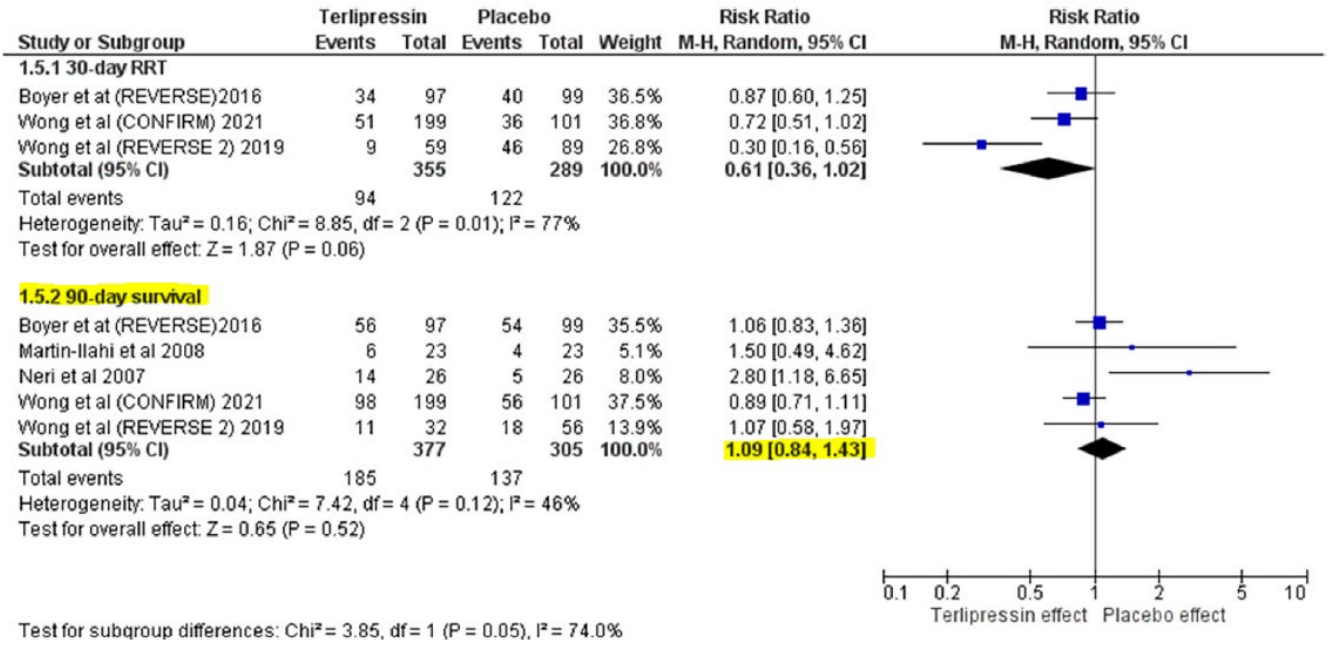
When reviewing the clinical efficacy, overall, reversal of HRS was the key benefit of terlipressin satisfactorily. Mohamed et al. (2021) estimated the relative risk (RR) of HRS reversal against placebo to 2.08; 95% CI [1.51, 2.86], P < 0.001). Other meta-analyses have reported similar results in favour of terlipressin (Allegretti, 2017, Facciorusso, 2017, Gifford, 2017, Zheng, 2017). For patients who may be a candidate for liver transplantation, reversing type 1 HRS is associated with better outcomes both pre- and post-transplant (Sanyal 2008, Gluud 2012, Hiremath 2013, Boyer 2016, Zheng 2017, Wang 2018). For the majority of type 1 HRS patients who are not candidates for liver transplant, reversing type 1 HRS 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, oesophageal variceal haemorrhage, and infection. Moreover, the benefit of terlipressin treatment was further analysed in 3 important subgroups: subjects with alcoholic hepatitis, subjects with systemic inflammatory response syndrome, and subjects with low MAP (<70 mm Hg) at baseline. There was a higher incidence of type 1 HRS reversal with terlipressin treatment in all 3 of these difficult-to-treat subgroups compared with placebo (Mallinckrodt Pharmaceuticals Briefing document, 2020). Additionally, terlipressin treatment is associated with additional clinical benefits, including decreased incidence of RRT and decreased length of ICU stay, according to the CONFIRM trial.

In contrast, survival has not been satisfactorily demonstrated as a benefit. Before the publication of CONFIRM, meta-analyses showed no significant survival benefit, albeit all showed a tendency in favour of terlipressin (Allegretti, 2017, Facciorusso, 2016, Gifford, 2017).

In a meta-analysis by Facciorusso et al. (2016) it was concluded that moderate-quality evidence might support the use of terlipressin over placebo for reduction of short-term mortality (OR 0.65, 95% CI 0.41–1.05). In a meta-analysis by Gifford et al. (2017) a tendency of mortality benefit favouring terlipressin was found (RR:0.79, 95%CI:0.63-1.01), but sensitivity analysis including only trials with low risk of selection bias weakened this relationship (RR:0.87,95%CI:0.71-1.06). In a meta-analysis by Allegretti (2017), a borderline statistically significant reduction in mortality was found (upper limit of CI close to 1: RR 0.78 [0.63,0.98]. See also forest plot below). This review suggests that terlipressin may be associated with beneficial effects on mortality and renal function in people with cirrhosis and type 1 HRS, but it is also associated with serious adverse effects. The strength of the evidence was downgraded to low-quality of evidence due to methodological issues including bias control, clinical heterogeneity, and imprecision. Consequently, the authors concluded, that additional evidence is

needed. In the meta-analysis by Mohamed et al. (2021) which included the CONFIRM study (but REVERSE patients were entered twice, which warrants caution), no difference in 90-day survival was found (RR 1.09; 95% CI (0.84, 1.43), P = 0.52) [Figure 15]. CONFIRM adds to the existing evidence base with a relatively heavy weight since it is larger than all existing studies.

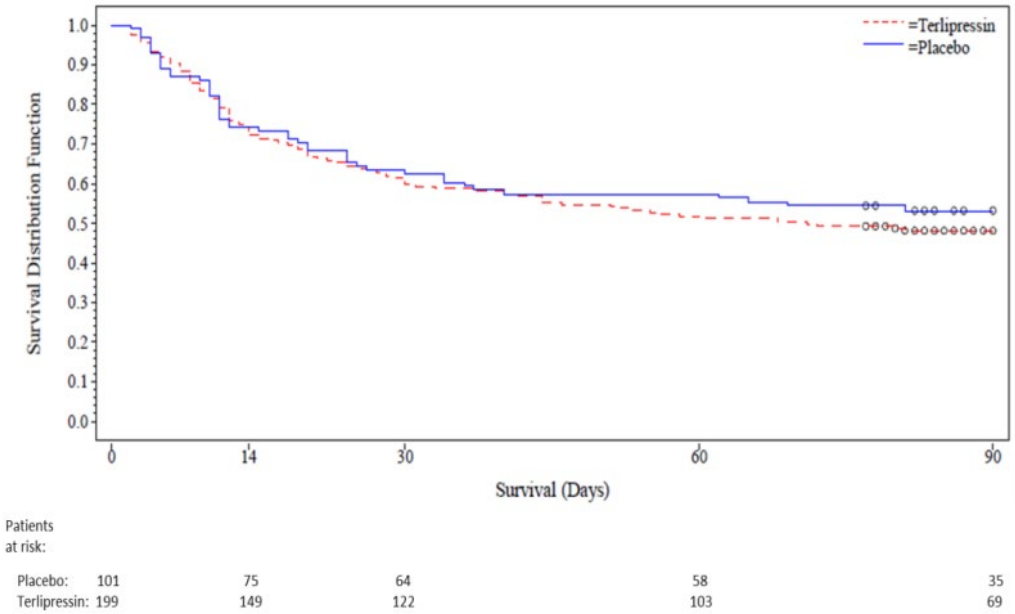
Figure 15 - Meta-analysis: 90-day survival.



Source: Mohamed, 2021 (Figure 5)

Thus, the benefit on the outcome 90 days survival is uncertain. Moreover, according to pooled OT-0401, REVERSE and CONFIRM data, no indications of benefit could be seen at any timepoint until 90 days. Timing of death is also important to consider, since prolonging life even by a few days could be beneficial for some patients. A K-M plot of the survival data from CONFIRM indicates no apparent difference in survival at any time point during the study (Figure 15).

Figure 16 – Overall survival (days) in the terlipressin vs placebo group, CONFIRM trial



Source: Wong, 2021 (Figure S6A)

Based on the combined data from OT-0401, REVERSE and CONFIRM studies, data on timing of death do not indicate any differences in survival between terlipressin and placebo at any time point during the study durations. Across pooled trials (OT-0401, REVERSE, CONFIRM), 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 trial in both treatment groups compared with OT-0401 and REVERSE trials. In the CONFIRM trial, 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 between-group difference of 5.6%. This finding was not replicated in the other two trials where rates of transplantation were similar between treatment arms.

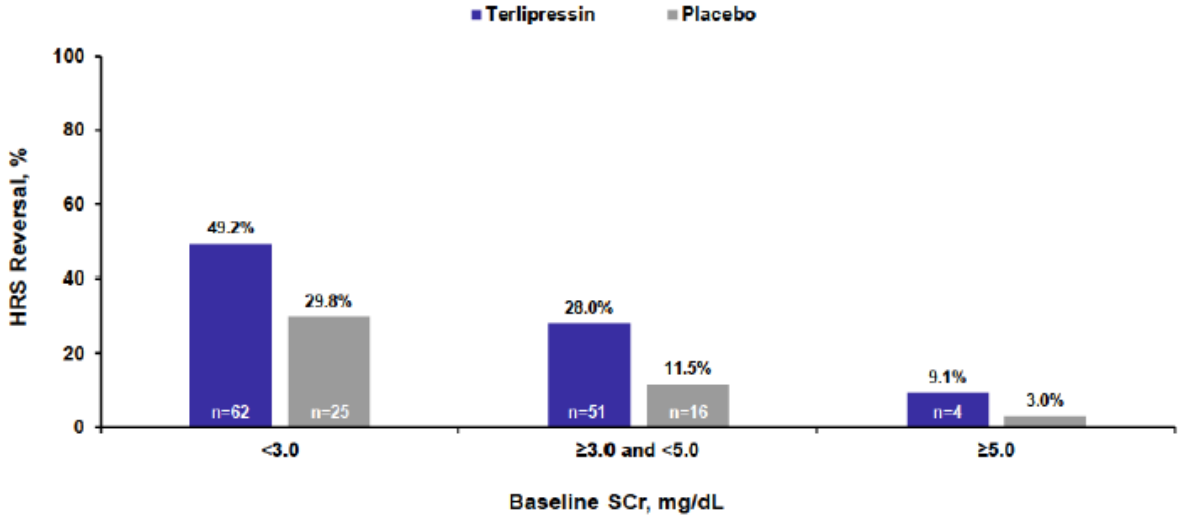
Subgroup analysis

Baseline serum creatinine (sCr)

Based on the combined data from OT-0401, REVERSE and CONFIRM studies, the impact of baseline serum creatinine (sCr) on the efficacy of terlipressin and albumin for the treatment of HRS type 1 showed that a higher sCr value at the beginning of treatment was associated with lower probability of response to treatment and poor survival (Mallinckrodt Pharmaceuticals Briefing Document, 2020). Response rates decreased stepwise with increases in creatinine. The likelihood of HRS reversal in either treatment arm (terlipressin + albumin vs. placebo + albumin) was greatest in those with sCr levels of <3.0 mg/dl, less so in those with sCr of 3.0 to 5.0 mg/dl, and least in those with sCr >5.0 mg/dl.

Similarly, the treatment effect of terlipressin vs. placebo was greatest in patients with sCr <3.0 mg/dl at the beginning of treatment with a 19.4% absolute difference in HRS reversal between the terlipressin and placebo groups, compared to a difference of 16.5% in the patients with sCr values of 3.0 to 5.0 mg/dl at the beginning of treatment, and a difference of 6.1% for patients with sCr >5.0 mg/dl at the beginning of treatment (Figure 17).

Figure 17- HRS reversal by serum creatinine category in the pooled ITT population



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

Source: Mallinckrodt Pharmaceuticals Briefing document, 2020 (Figure 18)

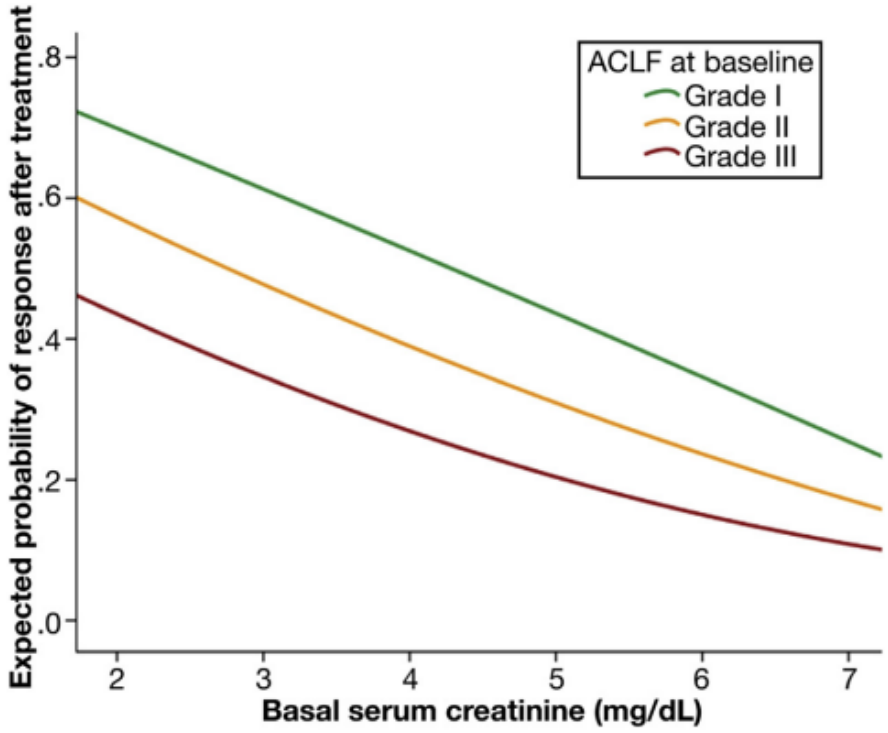
In CONFIRM, enrolled patients had baseline mean (±standard deviation) sCr of 3.5 ± 1.0 mg/dl (range between 2.25 mg/dL and 7.0 mg/dL prior to randomization). To understand how well this patient population compares to real world patients in the EU, two references have been identified: In a real-world cohort on 225 type 1 HRS patients from 26 medical centres in the UK the baseline sCr was 3.25 ± 1.64 mg/dL at vasopressor initiation (90% terlipressin-treated) (Moore, 2020). In another observational study on 298 terlipressin-treated HRS patients across several European countries, baseline median sCr (±IQR) was 2.9 (2.5-3.6) at terlipressin initiation (Piano, 2018). Hence, patients in the study by Moore et al. appeared overall comparable to the CONFIRM population on this parameter, whereas patients in the study by Piano et al. generally had lower baseline sCR at treatment initiation. Both Piano et al and Moore et al found that prognosis was more favourable in patients with mild acute kidney injury.

In conclusion, from the data of CONFIRM, REVERSE and OT-0401, patients with baseline sCr above 5 mg/dL had substantially reduced likelihood of achieving type 1 HRS reversal 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 as well as reduced survival than those treated with placebo. An important limitation of this finding is that it is based on post hoc analysis and thus carries a risk of biased outcome and threshold selection.

Patients with ACLF score 3

In a study by Piano et al. (2018) in which they performed a retrospective analysis of 4 different cohorts of consecutive patients with HRS treated with terlipressin and albumin from February 2007 through January 2016 in the EU. These studies did not include the OT-0401, REVERSE and CONFIRM studies. Of patients with ACLF grade 1, 60% responded to treatment; among those with ACLF grade 2, 48% responded, and among those with ACLF grade 3, 29% responded (P < 0.001 for comparison between grades). In multivariate analysis, baseline serum level of creatinine (odds ratio, 0.23; P [.001) and ACLF grade (odds ratio, 0.63; P 0.01) were independently associated with response to treatment. The same study showed that the probability of HRS resolution decreased stepwise from ACLF-1 to ACLF-3 at any level of sCr (Figure 18).

Figure 18 – Probability of response to treatment with terlipressin and albumin according to baseline serum creatinine in patients with CLF grade 1, 2 and 3

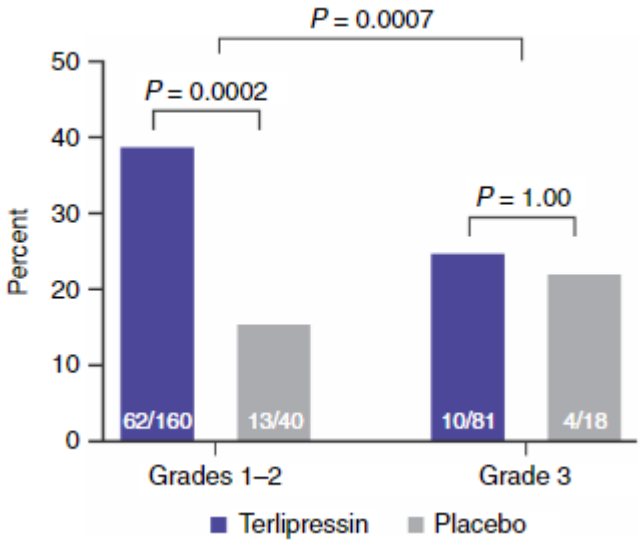


Source: Piano, 2018 (Figure 1)

However, a small number of patients with high-grade ACLF do respond to terlipressin with reversal of HRS1.

Reduced efficacy in patients with ACLF grade 3 was observed in the post-hoc analysis by Wong et al (2022). When patients were separated into grades 1–2 and grade 3 ACLF subgroups, there was a significant difference in the rates of HRS reversal in the ACLF grades 1–2 versus the ACLF grade 3subgroup (p= 0.0007). The use of terlipressin was only able to achieve an increased HRS reversal rate versus placebo in the ACLF grades 1–2 subgroup (p= 0.0002), but this was not observed in the grade 3 ACLF subgroup (Figure 19).

Figure 19 – Renal failure reversal by ACLF grade with terlipressin versus placebo



Source: Wong, 2022 (Figure 1)

2.3.1. Discussion on efficacy

As outlined in the section above, the key benefit satisfactorily demonstrated is reversal of HRS. Mohamed et al. (2021) estimated the relative risk (RR) of HRS reversal against placebo to 2.08; 95% CI [1.51, 2.86], P< 0.001). Other meta-analyses have reported similar results in favour of terlipressin (Allegretti, 2017, Facciorusso, 2017, Gifford, 2017, Zheng, 2017). Terlipressin treatment is associated with additional clinical benefits, including decreased incidence of RRT and decreased length of ICU stay, according to the CONFIRM trial. For patients who may be a candidate for liver transplantation, reversing type 1 HRS is associated with better outcomes both pre- and post-transplant (Sanyal, 2008, Gluud, 2012, Hiremath, 2013, Boyer, 2016, Zheng, 2017, Wang, 2018). For the majority of type 1 HRS patients who are not candidates for liver transplant, reversing type 1 HRS 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).

On the other hand, the survival benefit of terlipressin treatment in type 1 HRS remains uncertain. Before the publication of CONFIRM, meta-analyses showed no significant survival benefit, albeit all showed a tendency in favour of terlipressin (Allegretti, 2017, Facciorusso, 2016, Gifford, 2017). CONFIRM adds to the existing evidence base with a relatively heavy weight since it is larger than all existing studies. Accordingly, the single meta-analysis in which CONFIRM is included, no difference in survival between terlipressin and placebo was found (RR 1.09; 95% CI (0.84, 1.43), p= 0.52; Mohamed 2021). Thus, the benefit on the outcome 90-day survival is uncertain. Moreover, according to pooled OT-0401, REVERSE and CONFIRM data, no indications of survival benefit could be seen at any timepoint until 90 days.

3. Expert consultation

The PRAC consulted the AHEG which provided advice on a number of issues. Firstly, the experts agreed on the place of terlipressin in EU as a fundamental and first line of treatment for type 1 HRS, a condition with limited treatment options. While discussing the findings from the US trials and the representativeness for the EU setting, the experts expressed difficulty to extrapolate the US data. Specifically in view of the CONFIRM trial, differences both in treatment and diagnosis of HRS between EU and US were highlighted:

- Type of patients treated in the CONFIRM trial. The available data shows that patients in this trial were in more advanced stages, revealed by high sCR levels. These observed levels may explain a higher complication rate since impaired kidney function in general impairs a favourable outcome. The study patients have been already pre-treated with vasopressors. Additionally, patients were also apparently hospitalized for longer times and extensively pre-treated with albumin before being referred to the study centre entering the trial and initiating treatment with terlipressin. Distinctively, experts revealed that in the majority of EU centres patients are referred earlier and therefore receive terlipressin in earlier stages of the disease. For Europe, while there is currently no published data on sCR levels at which treatment with terlipressin is to be started, experts considered that in EU clinical practise start of treatment would be at around a sCR 1.5 – 2.5 mg/dl.
- Duration of treatment. Terlipressin was used in a shorter duration in CONFIRM trial as, per trials' protocol, treatment was stopped for a numerous of reasons such as transplantation, occurrence of adverse event, haemodialysis need, etc. It is also understood that, in the study,

terlipressin was stopped according to the protocol when creatinine levels did not decrease despite treatment, potentially leading to a shorter treatment duration than in clinical practice.

- Albumin level. The experts considered the mean serum albumin levels in the CONFIRM trial higher than expected to be in EU clinical practise. The experts shared their view that patients in the trial appeared to be overtreated with albumin before treatment with terlipressin was initiated and had already received different vasopressors before entering in the study centre which might explain the observed severe adverse events.

The different safety results based on the sCR level were noted. However, experts considered that data from the post hoc analysis does not allow to make strong conclusions. Additionally, the cut-off value of sCR 5 mg/dl had been chosen arbitrarily and more data would be needed on a patient level to define a clear threshold for risk mitigation based on sCR only. The experts agreed that less response to terlipressin treatment is expected in patients with high sCR, but these patients could still benefit from terlipressin. More concerns over the ACLF grade impact than sCR were expressed.

Regarding the respiratory events, the experts acknowledged the risk of type 1 HRS patients treated with terlipressin to develop volume overload. As noted before, patients in the CONFIRM trial received high doses of prior albumin which is a risk of volume overload in the circulation. Patients with higher levels of albumin are at higher risk of pulmonary oedema and pulmonary oedema has been observed in clinical trials with albumin already at levels of around 3.2 g/dl. Experts agreed that a warning on monitoring of fluid overload is warranted in accordance with treating centres protocols adapting treatment with albumin and diuretics accordingly. As conclusion, the experts recommended that overtreatment with albumin should be avoided to manage the risk of pulmonary oedema. They advised to stress adherence to the EASL guidelines regarding the albumin amount per day to be used i.e., 1g/kg every day for 2 days before starting treatment with terlipressin and a low level of albumin during terlipressin treatment (20-40 g/day).

For sepsis and infections events, experts referenced the EU guidelines recommending monitoring before terlipressin treatment as well as throughout treatment if data is suggestive (e.g., in case of worsening of the patient condition).

Contraindicating terlipressin treatment in patients with serious cardiovascular, respiratory or infectious diseases was also discussed. The experts expressed that they would favour warnings on these diseases instead of contraindications given the complexity of the individual clinical setting. Warnings would not restrict the access to terlipressin to these patients and allow the physician's decision on the best way to manage the HRS patients.

The experts considered that information on the risks of sepsis and respiratory failure should be added to the product information. As for risk groups, the experts stated that a cut-off value for sCR is difficult to define but given the differences in outcome revealed by the post hoc analysis, a warning referring to sCr ≥ 5 mg/dl could be added to the product information (not a contraindication). The final threshold of sCR should be left for the physician discretion in the management of these patients.

Relative to the ACLF grade 3 and MELD score, experts considered preferable to add a warning instead of a contraindication as data is retrieved from post hoc analysis and the definition of ACLF was not available for 2 of the trials considered in the analysis.

It was considered that a warning on the monitoring of fluid overload would make sense, but processes should be according to treating centre's protocols. CVP could be proposed as a tool for monitoring fluid overload, but recommendations should be kept general as standard monitoring would be sufficient in most of the patients and treatment on ICU would often not be necessary for patients with milder disease.

Concerning the method of administration, experts revealed that in the EU, continued infusion is usually applied. The current data available suggest that continued infusion leads to a more stable exposure of terlipressin, with a low dose given during 24 hours (compared to bolus injections), and less adverse events expected in consequence. However more data in terms of efficacy and safety from well-powered studies would be needed to quantify clear advantages of this method of administration. Experts agreed that an inclusion of a recommendation to use continuous intravenous infusion is appropriate to reach for a more stable exposure of terlipressin and possibly less AEs expected in consequence.

From the patient's perspective it is understood that these patients are in various serious conditions and rely on the physicians' knowledge on the best care to receive, however there is a gap in the information available to patients on the appropriate method of administration of terlipressin, e.g., in the product information.

4. Benefit-risk balance

The benefit of terlipressin in treatment of type 1 HRS is considered established based on evidence from clinical trials and meta-analysis showing a consistent effect of terlipressin on type 1 HRS reversal compared to placebo and midodrine/octreotide. The new data from the CONFIRM trial supported the established efficacy of terlipressin in treatment of type 1 HRS on the outcome of reversal of type 1 HRS. In addition, other meta-analyses were identified with reported similar efficacy results in favour of terlipressin. However, pooled data from the Mallinckrodt studies (OT-0401, REVERSE and CONFIRM) indicated no statistical differences in survival between terlipressin and placebo at any timepoint until 90 days. Accordingly, the single meta-analysis in which CONFIRM is included, found no difference in survival between terlipressin and placebo. PRAC considered that this finding is a concern as the most relevant outcome for type 1 HRS patients is to prolong the window of opportunity for a liver transplant through an increase in survival. However, there is some level of uncertainty regarding the survival outcome, as the results differ amongst the evidence (trials and meta-analysis) reviewed, due to the heterogeneity of the studies and depending on the specific selection criteria applied in the meta-analyses. A few of the smallest randomised controlled trials (RCTs) conducted do indicate a non-significant survival benefit favouring terlipressin, whereas the largest RCTs do not. Hence, when combined and weighted according to study sizes, the survival benefit seems to disappear.

When assessing the risk factors for a reduced or non-response to terlipressin treatment, it was observed that the proportional effect of terlipressin on HRS reversal appeared reduced when used to treat patients with baseline sCr above 5 mg/dl. Moreover, in the pooled data from the studies OT-0401, REVERSE, CONFIRM, patients with baseline sCr above 5 mg/dl experienced a 2-fold increased risk of death compared to placebo after 14 days. In absolute measures, it is a 27.2% difference in mortality favouring placebo treatment, and therefore patients with advanced renal dysfunction with creatinine levels above 5 mg/dl did not benefit in the study from treatment with terlipressin. PRAC discussed the prognostic ability of the threshold (sCr above 5 mg/dl) to predict an unfavourable outcome for the individual patient and considered that patients with type 1 HRS treated with terlipressin are complex and their prognosis will most likely also depend on many other important prognostic factors including e.g. age, cause of cirrhosis (e.g. alcoholic or non-alcoholic), and comorbidities. Similarly, from the post-hoc analysis of the CONFIRM trial by Wong et al (2022), reduced efficacy and increased mortality was observed in patients with very advanced liver disease defined as ACLF grade 3. PRAC noted that these are post-hoc analyses which need to be interpreted with caution. Additionally, it was noted that the treatment decisions for individual cases of type 1 HRS should be left at the discretion of the clinician, as these patients are being treated according to their

individual circumstances in an advanced expert setting. This was supported by the experts consulted by PRAC during the procedure. In line with the observations and the discussion, PRAC was of the view that the data reviewed raises concerns about the benefit and risk of terlipressin treatment in specific groups of patients, and therefore PRAC considered that a warning statement to avoid terlipressin treatment in patients with baseline sCr levels above 5 mg/dl and/or ACLF grade 3 should be implemented in the product information (SmPC 4.2 and 4.4 and respective PL sections).

The safety data assessed revealed that mortality up to Day 90 was greater in the terlipressin as compared to the placebo arm in the CONFIRM trial. Fatal AEs associated with respiratory failure, sepsis and septic shock were reported in a higher percentage of subjects in the terlipressin arm in the CONFIRM study; analyses of the pooled study data revealed similar findings. The most commonly reported respiratory AEs in the terlipressin arm were respiratory failure, dyspnoea, pulmonary oedema and pleural effusion and these events were reported at a higher incidence in the terlipressin than in the placebo arm. Based on the pooled data from the 3 trials reviewed, PRAC observed that the incidence of respiratory failure and related AEs in the terlipressin arm was markedly higher than the estimated incidence according to the current SmPC section 4.8, where e.g., respiratory failure is currently listed with frequency uncommon. PRAC therefore considered that the frequencies of the adverse reactions 'respiratory failure', 'pulmonary oedema', 'respiratory distress', 'dyspnoea' should be updated in the product information. Monitoring of the occurrence of these reactions was discussed. Experts agreed that a warning on monitoring of fluid overload is warranted in accordance with treating centres' protocols adapting treatment with albumin and diuretics accordingly, while no clearly defined protocol or tool could be identified. The product information should include wording to instruct prescribers and patients on the requirements of regular monitoring to consider during treatment (blood pressure, heart rate, oxygen saturation, serum levels of sodium and potassium, as well as fluid balance) and the particular care required in the management of patients with cardiovascular or pulmonary disease. Additionally, instructions should be added to not start treatment with terlipressin in patients with a new onset of breathing difficulties or worsening of respiratory disease and to discontinue treatment if respiratory failure symptoms are severe or do not resolve (SmPC 4.4 and respective PL section(s)).

Risk factors for the development of respiratory events were also assessed. According to a post hoc subgroup analysis of the CONFIRM trial, the group of patients with severe reduction in liver function, in particular patients with ACLF grade 3 and MELD score $\geq$ 39, had the highest risk difference for developing respiratory failure and fluid overload-related SAEs when treated with terlipressin compared to placebo. The mechanism between severely reduced liver function and increased sensitivity to terlipressin-induced respiratory disorders is at present not clear, and the association could be confounded by other factors. PRAC noted that these are post-hoc analysis which need to be interpreted with caution. Additionally, and similarly to the conclusions regarding reduced benefit in these patient subgroups, it was noted that the treatment decisions for individual cases of type 1 HRS should be left at the discretion of the clinician, as these patients are being treated according to their individual circumstances in an advanced expert setting. This was supported by the experts consulted by PRAC during the procedure. In line with the observations and the discussion, PRAC was of the view that the data reviewed raises concerns about the risk associated with terlipressin treatment in specific groups of type 1 HRS patients, and therefore concluded there is value in the inclusion of a warning in the product information regarding the association between ACLF grade 3 and/or MELD score $\geq$39 and the development of respiratory failure and thus increased mortality (SmPC 4.4 and respective PL section(s)).

The modifying role of albumin in the terlipressin-respiratory failure association was also discussed. Patients with high serum albumin levels are presumed to be at higher risk of respiratory failure when treated with terlipressin. In the CONFIRM trial, prior albumin was used in larger doses than what is recommended in the EASL guidelines and as reported by the experts consulted in the review, which

may have contributed to the above safety findings. PRAC considered that given the differences in the practice reported between US and EU and since albumin is part of the standard of care, and terlipressin effectiveness depends on albumin infusion, no measure is considered needed regarding the concomitant use of albumin. It is however relevant to strengthen the product information of terlipressin products to recommend caution when terlipressin is administered together with human albumin and consider dose reduction of human albumin in case of signs or symptoms of respiratory failure or fluid overload (SmPC 4.4 and respective PL section(s)).

Based on the imbalance of sepsis/septic shock cases between the terlipressin arm and the placebo arm in all 3 trials, the fact that the risk difference (RD) of 7% (95% CI = 3.5, 10.5) in the CONFIRM trial is statistically significant and that sepsis/septic shock is a serious event and a potential fatal complication for these patients (60% of the patients with sepsis in the CONFIRM trial died of the event), PRAC considered sepsis/septic shock an important identified risk of terlipressin that should be added to the product information as a listed adverse reaction together with a warning to prescribers and patients on these events. Additionally, the product information should include instructions for daily monitoring for any symptom suggestive of infection (SmPC 4.4 and 4.8 and respective PL sections).

The evidence on the alternative method of administration by continuous intravenous (IV) infusion was considered. The MAHs provided information of several studies[2] published in the literature investigating the effect of continuous IV infusion of terlipressin in type 1 HRS in various settings. PRAC noted that the data on the safety and efficacy of continuous infusion is limited, especially in studies comparing continuous infusion to bolus injection. Even so, based on the reviewed studies from the literature, and specifically in the largest study identified (Cavallin, 2016), continuous intravenous infusion of terlipressin shows response to treatment comparable to the intravenous bolus of terlipressin and lower adverse events rates. During clinical studies, the starting dose was 2 mg/day. If no response to treatment was observed, the dose could be escalated up to a maximum of 12 mg/day. With these dosages, the rate of treatment-related adverse events was still low. Furthermore, the overall concentration of terlipressin in the blood was lower after intravenous infusion compared to the bolus. PRAC noted that the positive outcomes of the studies have led to inclusion of the continuous infusion in the clinical treatment guidelines (EASL, 2018) and clinical practice. Of note, these results are supported also by the clinical experience reported by AHEG. The AHEG experts described that their clinical experience support the current dosing recommendations of continuous IV infusion in clinical treatment guidelines (EASL 2018), as well as the two existing national SmPC updates regarding continuous infusion as alternative to bolus infusion already carried out in Italy and Austria.

Overall, despite the limitations in the evidence as outlined, PRAC considered that continuous IV infusion of terlipressin improves the overall safety profile to an extent that is clinically significant, while efficacy is not considered affected; the lower daily dose of terlipressin combined with more stable plasma concentrations associated with continuous infusion may improve the safety profile while still achieving similar response rates. PRAC considered that the observed reduction of overall treatment-related severe AEs (as predefined by Cavallin, 2016.) for continuous infusion could be extrapolated specifically to SAEs of respiratory disorders and sepsis concerned in the safety review. However, uncertainty remains if this administration method can reduce the risk of respiratory failure and sepsis compared to bolus injection. In light of the assessed data, PRAC is of view that the product information should be updated to recommend continuous infusion as an alternative to bolus administration. Additionally, clear dosing recommendations are warranted in section 4.2 of the SmPC to avoid medication errors.

[2] Halimi, 2002; Angeli, 2006; Angeli, 2008; Gerbes, 2009; Cavallin, 2015; Cavallin, 2016; Arora, 2020; Kulkarni, 2022.

A direct healthcare professional communication was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures agreed as described above.

In view of the above, the Committee considers that the benefit-risk balance of terlipressin-containing medicinal products indicated for the treatment of type 1 HRS remains favourable subject to the agreed amendments to the product information.

5. Summary of new activities and measures

5.1. Risk management

The Committee, having considered all information and data submitted in the procedure, recommends a series of pharmacovigilance activities and risk minimisation measures to further characterise and minimise the risk of respiratory failure and sepsis/septic shock.

Each MAH of terlipressin for which a risk management plan is in place should update their RMP to reflect the pharmacovigilance activities and risk minimisation measures listed below, as applicable, and submit it to the relevant NCA through an appropriate procedure.

5.1.1. Safety concerns

The Committee considered that the following safety concerns should be added as important identified risks: 'respiratory failure'; 'sepsis/septic shock'; 'increased mortality in patients with sCR ≥ 5 mg/dl at treatment initiation'; and 'increased mortality in patients with severe liver disease defined as ACLF grade 3 and/or MELD score ≥39'.

5.1.2. Risk minimisation measures

5.1.2.1. Routine risk minimisation measures

Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the events of respiratory failure and sepsis/septic shock associated with the use of terlipressin products indicated in the treatment of type 1 HRS. These changes include amendments to sections 4.2, 4.4, 4.8 and 5.1, of the SmPC.

Section 4.2 of the SmPC was updated to include continuous IV infusion as an alternative method of administration with the respective recommended posology.

Additionally, in section 4.2, information regarding the special populations 'hepatic impairment' and 'renal impairment' was added to include a recommendation to avoid treatment for type 1 HRS with terlipressin in patients with advanced renal dysfunction (defined by baseline sCR above 5 mg/dl) and severe liver disease (defined as ACLF grade 3 and/or MELD score ≥39). Section 4.4 was updated accordingly, to reflect the underlying data to justify the concerns with these special populations.

Warnings and precautions of use relating to the events of respiratory failure and sepsis/septic shock associated with the use of terlipressin products indicated in the treatment of type 1 HRS are recommend to reflect the current knowledge on the occurrence of these events, describe the appropriate monitoring and the measures to take in case of symptoms or signs of respiratory failure or sepsis/septic shock. Further warnings for caution when terlipressin is administered together with

human albumin and to consider dose reduction of human albumin in case of signs or symptoms of respiratory failure or fluid overload are included (section 4.4 of the SmPC).

Section 4.8 of the SmPC was updated to add 'sepsis' and add the new frequencies of the adverse reactions 'respiratory failure', 'pulmonary oedema', 'respiratory distress', 'dyspnoea' for the type 1 HRS indication, specifically.

Lastly, section 5.1. of the SmPC was updated to reflect the results of the main study supporting the inclusion of the continuous IV infusion as an alternative method.

The Package Leaflet was amended accordingly.

5.2. Direct Healthcare Professional Communications and Communication plan

The Committee adopted the wording of a DHPC, to inform healthcare professionals of the increased risk of respiratory failure and sepsis/septic shock with terlipressin products indicated in the treatment of type 1 HRS and associated risk minimisation measures, including the amendments to the product information. The Committee also agreed on a communication plan.

6. Grounds for Recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC resulting from the evaluation of data related to pharmacovigilance for terlipressin-containing medicinal products indicated in the treatment of type 1 HRS.
- The PRAC considered the totality of the data, including the clinical data from the CONFIRM trial, the pooled data for 3 trials (OT-0401, REVERSE, CONFIRM), and the data submitted by the MAH(s) in writing. The PRAC also considered the outcome of consultation with an ad-hoc expert group.
- The PRAC concluded, based on the available efficacy data (including data which became available since the initial marketing authorisation), that the evidence does not raise serious doubts on the established efficacy on the outcome of reversal of type 1 HRS, whereas the survival benefit remains uncertain.
- The PRAC also concluded that use of terlipressin-containing medicinal products for treatment of type 1 HRS is associated with an increased risk of respiratory failure and a risk of sepsis/septic shock. The PRAC noted the potential additive effect of concomitant use of albumin and terlipressin, as albumin itself is associated with a risk of volume overload and respiratory failure, and overall higher albumin doses were used in CONFIRM compared to the EU clinical guidelines.
- The PRAC recommended that the product information should be updated to take into consideration the current clinical knowledge on safety of terlipressin when used in the treatment of type 1 HRS with warnings and precautions regarding respiratory failure and sepsis/septic shock. The PRAC also recommended that a warning to use albumin when administered together with terlipressin with caution should be included in the product information.

- The PRAC was of the view that the data reviewed raises concerns about the benefit and the risk of terlipressin treatment in specific groups of patients, namely in patients with advanced renal dysfunction (defined by baseline sCR above 442µmol/l (5.0 mg/dl)) and severe liver disease (defined as ACLF grade 3 and/or MELD score ≥39), as the use of terlipressin in these patient groups is associated with an increased risk of mortality, reduced efficacy and increased risk of adverse events, including respiratory failure (specifically for patients with ACLF grade 3 and/or MELD score ≥39). The PRAC thus concluded that the product information should be updated to indicate that use of terlipressin in the treatment of type 1 HRS in patients with baseline sCR above 442µmol/l (5.0 mg/dl) or ACLF grade 3 and/or MELD score ≥39 should be avoided unless the healthcare professionals consider that the benefits of treatment with terlipressin outweigh the risks in the individual patient.
- The PRAC considered further evidence concerning the administration of terlipressin via continuous IV infusion, alternatively to the approved method of administration (bolus injection). Overall, while PRAC noted that the evidence available is limited, it is nevertheless indicative that continuous infusion improves the overall safety profile of terlipressin to an extent that is clinically significant, while efficacy is maintained. Therefore, as a risk minimisation measure, PRAC recommended the addition of continuous IV infusion to the product information, as an alternative method of administration.
- The PRAC also agreed on the dissemination of a direct healthcare professionals communication, together with a communication plan, to highlight the new information and the warnings relative to the identified risks added to the product information.

In view of the above, the Committee considers that the benefit-risk balance of terlipressin-containing medicinal products indicated in the treatment of type 1 HRS remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for terlipressin-containing medicinal products indicated in the treatment of type 1 HRS.

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