Terlipressin for the Treatment of Hepatorenal Syndrome Type 1: FDA Presentation

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Hepatorenal Syndrome Type 1 (HRS-1)

- Serious condition with high mortality rate
- Currently no approved therapies for treatment of HRS-1
- Liver transplant is the only definitive treatment when recovery of liver function is not feasible
  - However, transplant is often not feasible in the short-term
- Significant unmet medical need

Short-Term Management of HRS-1

- A number of interventions are used in clinical practice in an attempt to reverse the renal impairment, such as:
  - Albumin
  - Off-label pharmacologic interventions (e.g., midodrine, octreotide, norepinephrine)
- Goals of short-term management:
  - Improvement in renal function
  - Provide bridge to liver transplant for patients eligible for transplant

Outline

- Efficacy
- Safety
- Benefit-Risk profile

Points of Agreement with Applicant (1 of 2)

- CONFIRM study demonstrated an effect of terlipressin on the primary endpoint of verified hepatorenal syndrome (HRS) reversal:

  29% terlipressin vs 16% placebo (p=0.012)

Points of Agreement with Applicant (2 of 2)

Secondary endpoints for CONFIRM:

- The Hochberg procedure was used to control the familywise error rate for the 4 secondary endpoints
- CONFIRM demonstrated an effect of terlipressin on the first 3 secondary endpoints
- CONFIRM did not demonstrate an effect of terlipressin on the 4th secondary endpoint

	Terlipressin	**Placebo**	**p-value**
Hepatorenal syndrome (HRS) reversal (up to Day 14)	36%	17%	<0.001
HRS reversal without renal replacement therapy (RRT) to Day 30 ("Durability of HRS reversal")	32%	16%	0.003
HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup (up to Day 14)	33%	6%	<0.001
Verified HRS reversal without HRS recurrence by Day 30	24%	16%	0.092

Source: Study Report Tables 28, 29, 30, 31; verified by FDA

Verified HRS Reversal

- Verified HRS reversal is a putative surrogate endpoint
- Accepted as the primary endpoint for CONFIRM given the challenges of studying clinical outcomes in patients with HRS-1
- Accepted with the understanding that favorable trends in clinical outcomes thought to be predicted by successful treatment of HRS-1 would be expected

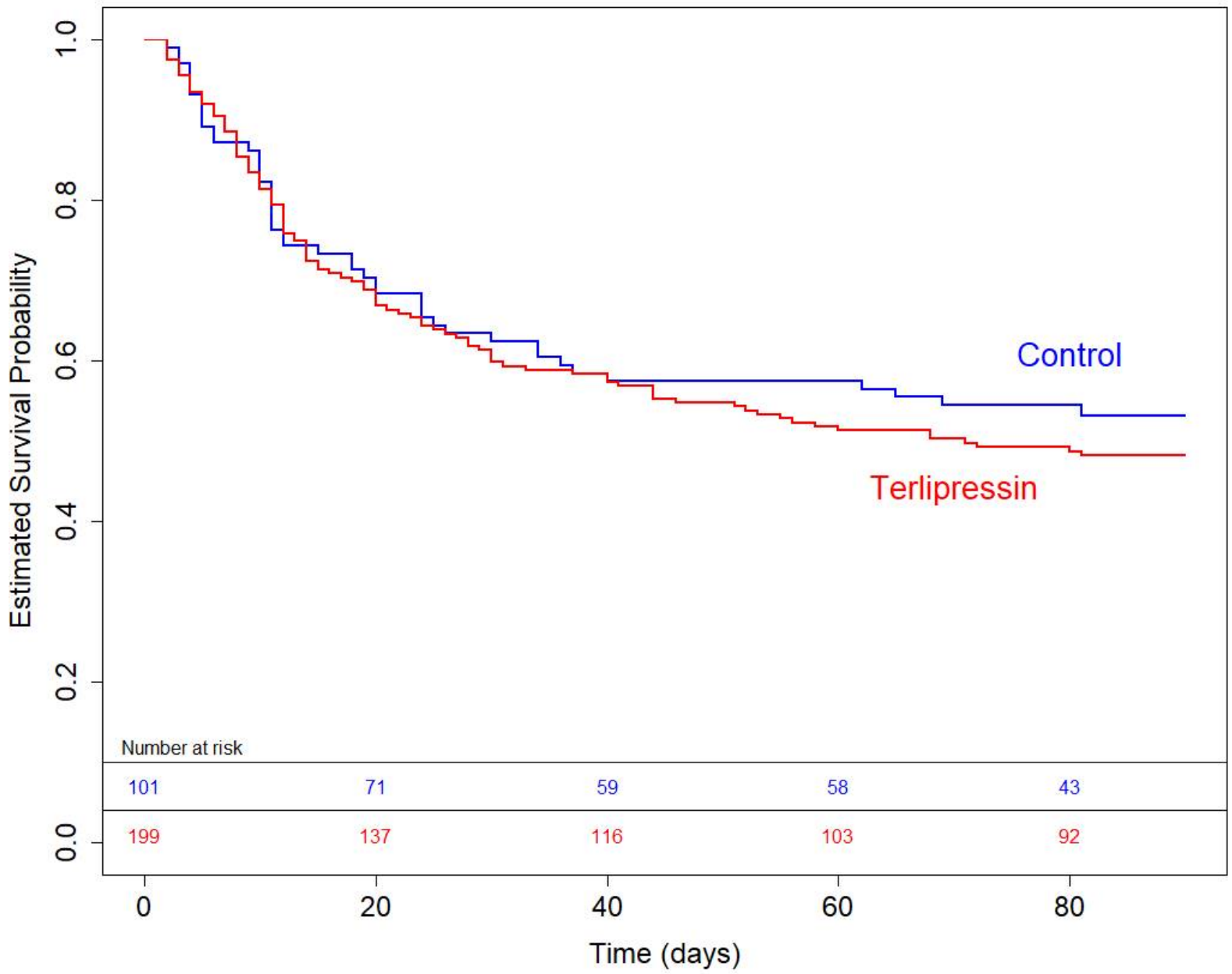
Exploratory Analyses of Treatment Effects on Clinical Outcomes Thought to be Predicted by HRS Reversal

- Investigated treatment effects on:
  - RRT initiation and/or survival
  - Outcomes post-liver transplant
  - Length of Intensive Care Unit (ICU) stay

Treatment Effects on RRT and/or Survival (to Day 90)

- RRT-free survival was slightly greater in the terlipressin as compared to the placebo arm
  - 34% on terlipressin vs 28% on placebo had RRT-free survival
- Treatment with terlipressin was associated with less use of RRT
  - 29% on terlipressin vs 39% on placebo initiated RRT
- Treatment with terlipressin was not associated with improved survival
  - 48% on terlipressin vs 53% on placebo survived

Probability of Survival Over Time to Day 90, Intent-to-Treat Population



Control

Terlipressin

Source: FDA Analysis

Exploratory Analyses of Treatment Effects on Clinical Outcomes Thought to be Predicted by HRS Reversal

- Investigated treatment effects on:
  - RRT initiation and/or survival
  - Outcomes post-liver transplant
  - Length of ICU stay

Summary of Liver Transplant by Day 90, Intent-to-Treat Population

	Terlipressin (n/N)	Placebo (n/N)
Listed for liver transplant at baseline	56/199 (28%)	20/101 (20%)
Did not receive a liver transplant by Day 90		
Died by Day 90	14/56 (25%)	0/20 (0%)
Alive by Day 90	8/56 (14%)	4/20 (20%)
Received a liver transplant by Day 90		
Died by Day 90	0/56 (0%)	1/20 (5%)
Alive by Day 90	34/56 (64%)	15/20 (75%)
Listed for liver transplant at any time	74/199 (37%)	35/101 (35%)
Received a liver transplant by Day 90	46/74 (62%)	29/35 (83%)

Source: Study Report, Table 14.3.4.17; verified by FDA

Treatment Effects on Post-Transplant Outcomes

- Reversing HRS prior to liver transplant is believed to be associated with improved survival and renal function post-transplant
- Analyzed RRT initiation or death post-transplant to Day 90

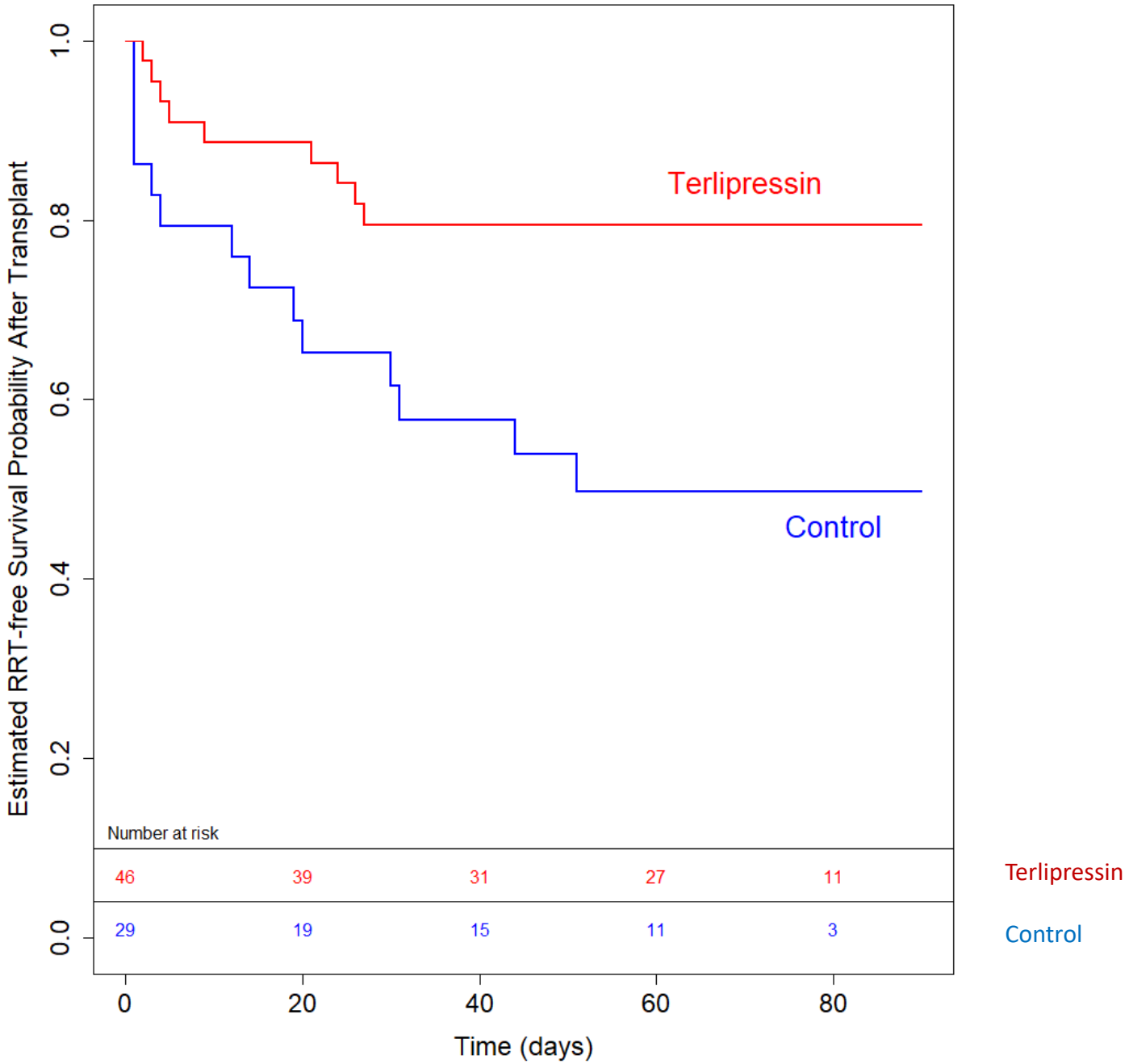
Initiation of RRT or Death After Receiving a Liver Transplant (to Day 90), Intent-to-treat Population

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

Source: FDA Analysis

RRT-Free Survival Over Time to Day 90 for Patients Who Received a Liver Transplant, Intent-to-Treat Population

(Time 0 is date of liver transplant)



Source: FDA Analysis

Limitation of Analyses

- Based on post-randomization variables, therefore, challenging to interpret

Exploratory Analyses of Treatment Effects on Clinical Outcomes Thought to be Predicted by HRS Reversal

- Investigated treatment effects on:
  - RRT initiation and/or survival
  - Outcomes post-liver transplant
  - Length of ICU stay

Treatment Effects on ICU Length of Stay (Initial Hospitalization)

- Analyses by Applicant
  - Similar proportion of patients admitted to ICU in each group:
    - 16% terlipressin vs 14% placebo
  - Terlipressin group had shorter average length of ICU stay:
    - Mean: 6.4 days terlipressin vs 13.5 days placebo
    - Median: 4.0 days terlipressin vs 8.0 days placebo

Limitations of Analyses

- Disposition of patients following ICU stay unknown
- Mortality data do not suggest benefit
  - 25/31 terlipressin patients (80%) who were transferred to the ICU died vs 9/14 placebo patients (64%)
- Average length of initial hospitalization was similar between the 2 groups
  - Mean: 24.5 days terlipressin vs 24.8 days placebo
  - Median: 19.0 days terlipressin vs 21.0 days placebo

Summary of Efficacy

- CONFIRM trial met its primary endpoint
- Favorable trend for less use of RRT for terlipressin group as compared to placebo
- No favorable trend for survival for terlipressin group
- Analyses of treatment effects on post-transplant RRT-free survival and ICU length of stay are challenging to interpret

Outline

- Efficacy
- Safety
- Benefit-Risk profile

Safety Evaluation of Terlipressin

- Focused on the known and potential toxicities of terlipressin based on its mechanism of action (MOA) and class effect
- Main safety data - CONFIRM
- Supportive safety data – a simple pooling of CONFIRM and two previous phase 3 studies – OT-0401 and REVERSE (Integrated Summary of Safety, ISS)

Known Toxicities or Potential Risks Based on Drug Class

- Terlipressin is a synthetic vasopressin analogue with weak selectivity (less than 2-fold) for vasopressin V1 receptors versus V2 receptors
- Key known risks based on terlipressin's effects on V1 receptors
  - Ischemic complications
  - Gastrointestinal (GI) symptoms and disorders
  - Respiratory effects
  - Bradycardia
- Potential risks based on effects on V2 receptors
  - Hyponatremia
  - Fluid retention

Key Safety Findings in CONFIRM

- Increased incidence and severity of respiratory failure AEs
- Increased incidence and severity of edema/fluid overload AEs
- Increased incidence of sepsis/septic shock serious adverse events (SAEs)
- Increased incidence of ischemia-associated events and gastrointestinal effects (e.g. abdominal pain)
- Mortality up to Day 90 was greater in terlipressin compared to placebo (51% vs. 44%)

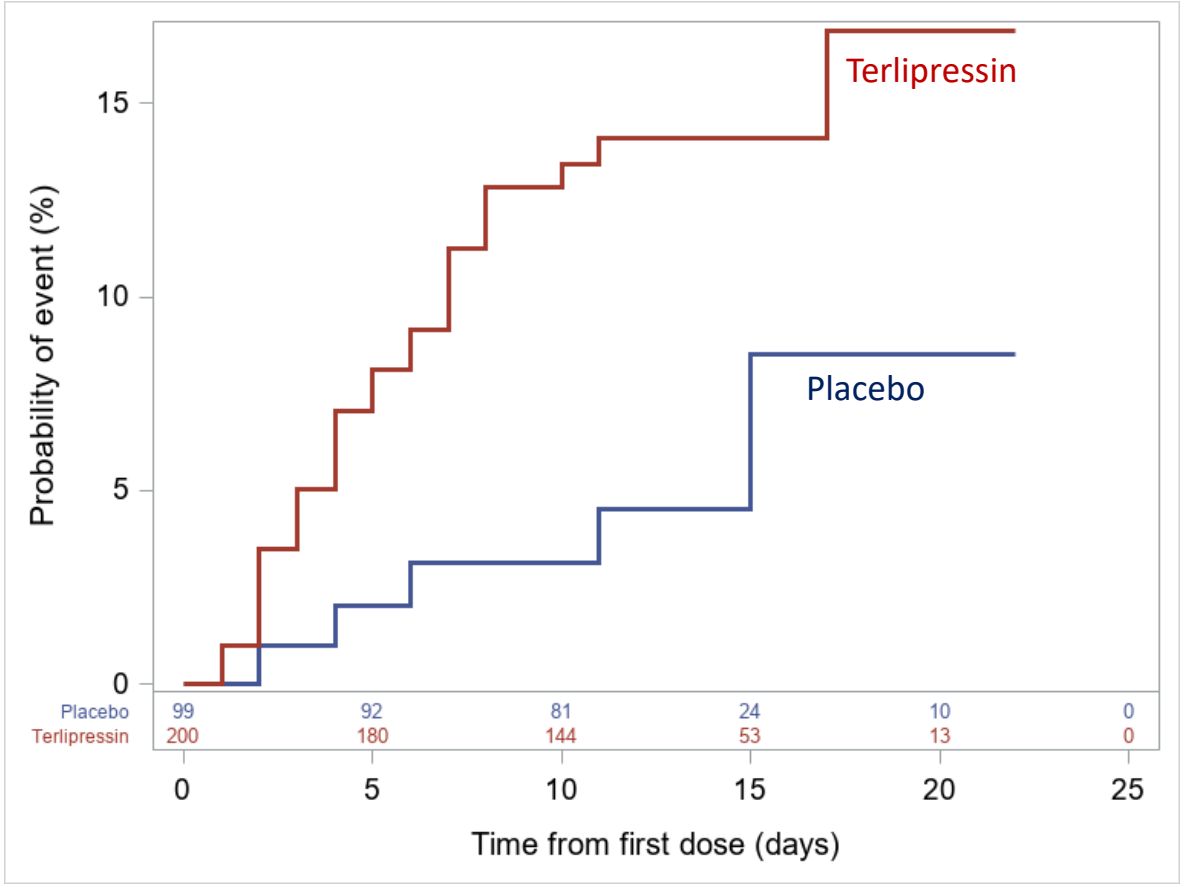
Main Safety Concern

- The seriousness of respiratory failure events
- The risk of fluid overload in the setting of albumin loading and the impact of fluid overload on the respiratory system
- Is the risk of respiratory failure predictable and manageable?

Respiratory Failure Serious Adverse Events

Risk difference (95% CI) = 8.9% (2.4, 15.4)

- Not a pre-specified event but review of the narratives supports the clinical significance of the event
  - More than three quarters of patients required an intervention such as intubation or bilevel positive airway pressure (BiPAP)
  - More than half of patients required care in the ICU
- The majority of the events occurred on treatment and > 50% occurred within 5 days
- Sixty-one percent of the events (17/28) in the terlipressin group had a fatal outcome; whereas one fatal event was reported in the placebo group (1/5, 20%)



Source: FDA Analysis

Respiratory Failure Serious Adverse Events

- Many events occurred in the setting of aspiration pneumonia/pneumonia or fluid overload (e.g., pulmonary edema, pleural effusion)
  - A higher frequency of fluid overload-related AEs was reported in the terlipressin than the placebo arm (28% vs. 16%)
  - 11/28 (39%) terlipressin-treated patients with respiratory failure SAEs also reported fluid overload-related AEs
- It is plausible that terlipressin could increase the risk of respiratory failure and fluid overload via effects on V1a and/or V2 receptors
- The etiology of the events is multifactorial. It is challenging to determine the role terlipressin may have played in any of the individual cases

The Incidence and Severity of Respiratory AEs Increased in Newer vs. Older Studies, Coinciding with Increased Use of Albumin for HRS Treatment

	OT-0401 (2004-2006)		REVERSE (2010-2013)		CONFIRM (2016-2019)	
	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

FDA Briefing Document, pg. 42

The Frequency of Fluid Overload-Related AEs was Greater in the Terlipressin Group than in the Placebo Group

	OT-0401 (2004-2006)		REVERSE (2010-2013)		CONFIRM (2016-2019)	
	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)

- Increased use of albumin may exacerbate hypervolemia
- The contribution of fluid overload to the respiratory failure events is possible
- Concomitant use of diuretics was approximately double in the terlipressin group vs. placebo (25.5% vs.13.1%) in CONFIRM

FDA Briefing Document, pg. 42

Management of Fluid Overload in CONFIRM

Per CONFIRM protocol

> *"…Subjects with increasing dyspnea, cough, orthopnea, or tachypnea should be carefully evaluated for evidence of pulmonary edema…."*
>
> *"In subjects with fluid overload, especially those with respiratory events…, careful assessment of concomitant albumin and temporary albumin dose reduction or discontinuance may be the most appropriate initial management…."*

- Despite the prespecified instructions, the increased risk of fluid overload and respiratory events was greatest in CONFIRM

Can the Risk of Respiratory Failure SAEs Be Predicted?

- Unclear whether patients at risk could be prospectively identified
  - Increased risk of serious respiratory failure events was generally consistent across demographic and disease characteristics
  - Respiratory events are multifactorial and can be related to underlying diseases
  - Will be difficult to discern terlipressin-related respiratory events from underlying disease in these complex patients

Sepsis Serious Adverse Events

Risk difference (95% CI) = 7% (3.5, 10.5)

- Sixty percent of these events resulted in death
- These serious event occurred evenly throughout the study with a median onset of 12 days
- Five patients (5/14, 36%) with a sepsis SAE also experienced a respiratory failure SAE in CONFIRM
- The increased risk of sepsis SAEs was also observed in the OT-0401 and REVERSE studies
- The mechanistic basis for the risk of sepsis is not immediately clear
  - Etiologic agents were predominantly bacterial
  - Could the risk of fluid overload and/or abdominal ischemia increase the risk of serious infection?

FDA's Position on the Applicant's Proposed Mitigation of Respiratory Failure and Related Respiratory and Sepsis Events

Mitigation strategy	Present in CONFIRM	Any data supporting the mitigation success?	FDA's position
Do not use in patients with serum creatinine ≥ 5 mg/dL Treat patients with hepatic encephalopathy score ≥ 3	N	Data do not support use of strategy	Increased risk of respiratory failure SAEs was observed with terlipressin regardless of baseline serum creatinine and hepatic encephalopathy score.
Stabilize patients with respiratory events. Manage fluid overload and pneumonia prior to treatment	N	None	HRS patients have a high background rate of dyspnea, fluid overload and pneumonia. It may be challenging to clinically implement.
Management of fluid overload (albumin, diuretics) during therapy Dose alteration if symptoms persist	Y	More respiratory failure SAEs (14% vs. 5%) and fluid overload-related AEs (28% vs. 16%) with terlipressin vs. placebo	The results of CONFIRM raise questions about the effectiveness of these instructions.
Dose reduction, interruption and discontinuation if worsening pneumonia	N	None	Mitigation related to pneumonia was not prospectively tested. The impact of this mitigation on clinical safety is uncertain.

FDA's Position on the Applicant's Proposed Mitigation of Respiratory Failure and Related Respiratory and Sepsis Events

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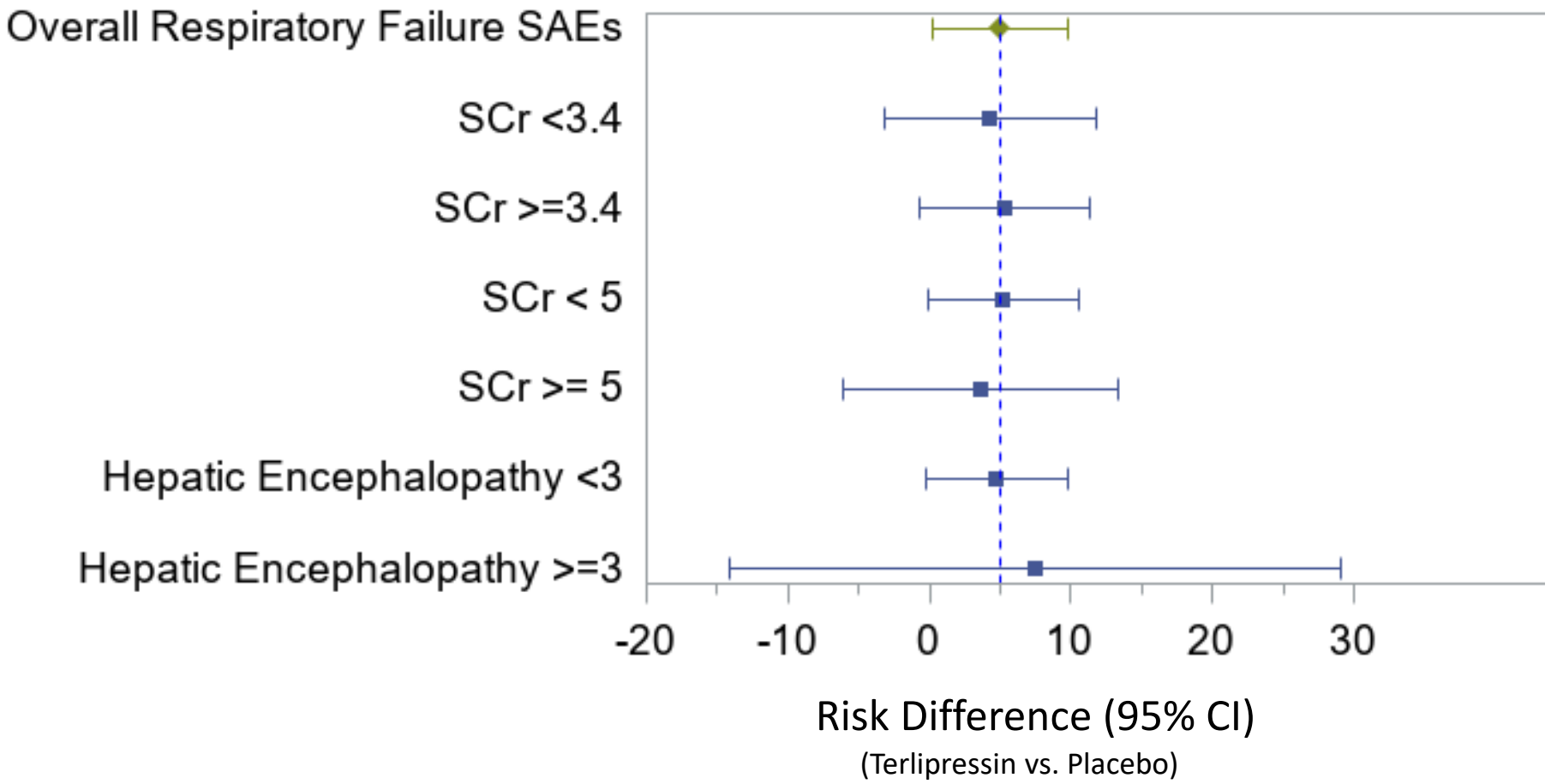
Do not use in patients with serum creatinine ≥ 5 mg/dL Treat patients with hepatic encephalopathy score ≥ 3	N	Data do not support use of strategy	Increased risk of respiratory failure SAEs was observed with terlipressin regardless of baseline serum creatinine and hepatic encephalopathy score.

Study Data Do Not Support the Mitigation Steps Utilizing Baseline SCr and Hepatic Encephalopathy Score



Source: FDA Analysis

Subgroup analyses conducted using ISS data

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Dose reduction, interruption and discontinuation if worsening pneumonia	N	None	Mitigation related to pneumonia was not prospectively tested. The impact of this mitigation on clinical safety is uncertain.

Summary of Safety

- Terlipressin causes adverse effects generally consistent with its MOA and class effects with an increased risk of certain serious adverse events
  - Most of the known risks appear manageable, however ischemic and respiratory events could lead to serious or fatal outcomes
  - Increased risk of serious respiratory failure is a major safety concern
  - Increased risk of sepsis was observed without a clear mechanism

- The risk of respiratory failure may not be reliably predicted and managed
  - The risk of fluid overload and associated albumin use complicate the clinical presentation and management of the event
  - There are multiple potential causes of respiratory failure and most of the risk mitigation steps proposed by the applicant have not been tested

Outline

- Efficacy
- Safety
- Benefit-Risk profile

Key Benefits and Risks (CONFIRM)

Benefits

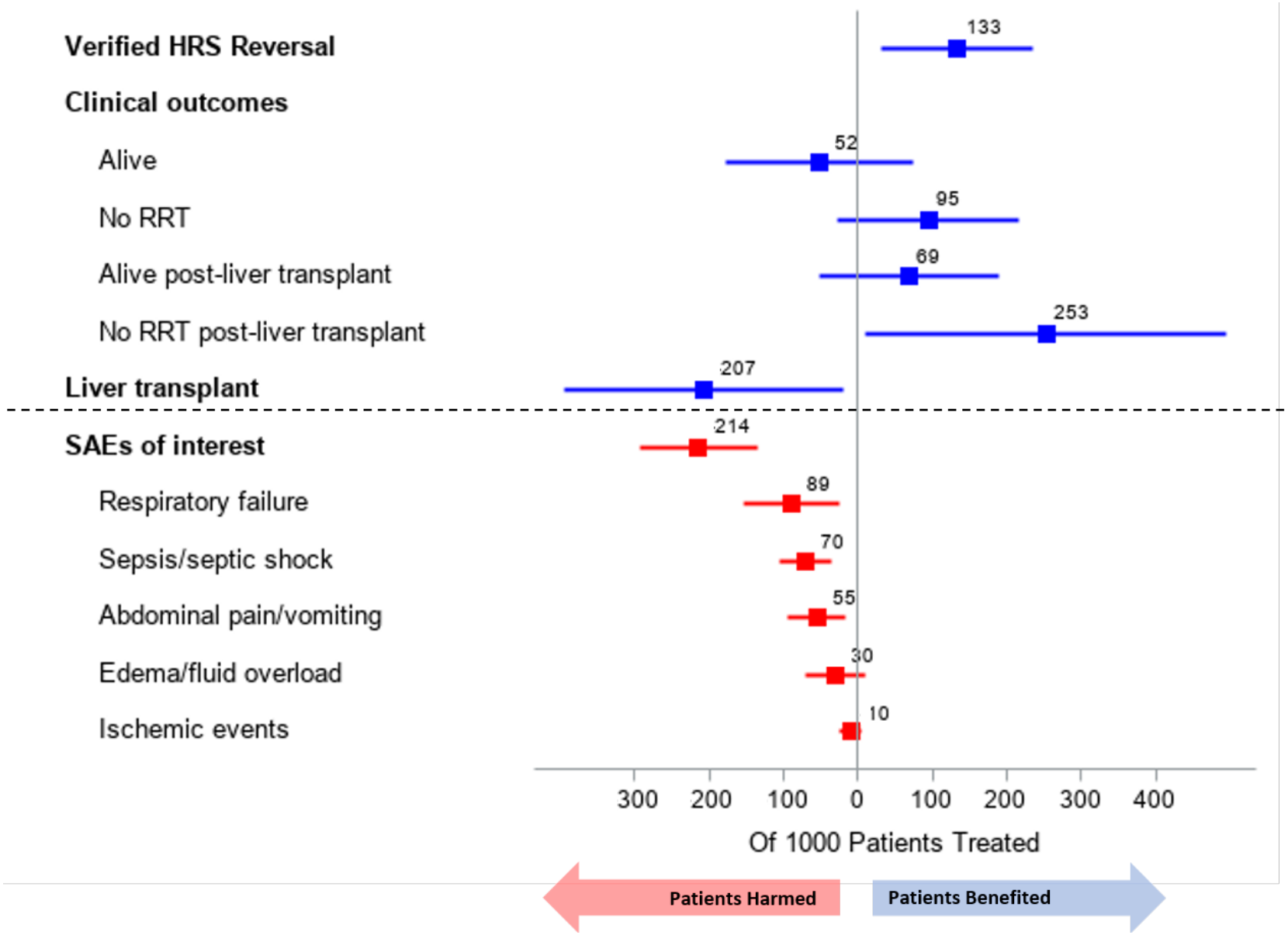
Benefits	Treatment Effect (%) Terlipressin vs Placebo
Verified HRS Reversal (putative surrogate endpoint)	13.3
Clinical outcomes possibly predicted by surrogate (Day 90)	
Alive	-5.2
No RRT	9.5
Alive post-liver transplant	6.9
No RRT post-liver transplant	25.3
Liver transplant (among patients listed at any point) (Day 90)	-20.7

Identified Risks

Risks (Through 30 Days After Last Dose)	Risk Difference (%) Terlipressin vs Placebo
SAEs of interest	21.4
Respiratory failure SAEs	8.9
Sepsis/septic shock SAEs	7.0
Abdominal pain/vomiting SAEs	5.5
Edema/fluid overload SAEs	3.0
Ischemia-related SAEs	1.0

Key Benefits and Risks (CONFIRM)

(Terlipressin vs Placebo)

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