Terlivaz®
terlipressin for injection

TERLIVAZ® (terlipressin) Clinical Outcomes and Value in the Treatment of HRS

INDICATION AND LIMITATION OF USE

TERLIVAZ is indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.

- Patients with a serum creatinine >5 mg/dL are unlikely to experience benefit.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

- **TERLIVAZ may cause serious or fatal respiratory failure. Patients with volume overload or with acute-on-chronic liver failure (ACLF) Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO_2) before initiating TERLIVAZ.**
- **Do not initiate TERLIVAZ in patients experiencing hypoxia (e.g., SpO_2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue TERLIVAZ if SpO_2 decreases below 90%.**

Contraindications

TERLIVAZ is contraindicated:

- In patients experiencing hypoxia or worsening respiratory symptoms.
- In patients with ongoing coronary, peripheral, or mesenteric ischemia.

Please see additional Important Safety Information throughout and on Page 9 and full Prescribing Information, including Boxed Warning, available at TERLIVAZ.com.

TERLIVAZ® Is FDA-approved for the Treatment of Adults With HRS With Rapid Reduction in Kidney Function Based on Data From the Landmark CONFIRM Phase 3 Trial[1]

- The *NEJM*-published phase 3 trial was the largest HRS trial globally to date[2]
- The multicenter, 2:1 randomized, placebo-controlled, double-blind trial was designed to evaluate efficacy and safety of TERLIVAZ to treat HRS in adult patients with rapid reduction in kidney function[1]
- Patients were enrolled based on a diagnosis of HRS[a] that included a rapid reduction in renal function (with trajectory for SCr to double within 2 weeks) to a **SCr ≥2.25 mg/dL** without sustained improvement in renal function after diuretic withdrawal and albumin challenge[1]

Inpatient setting

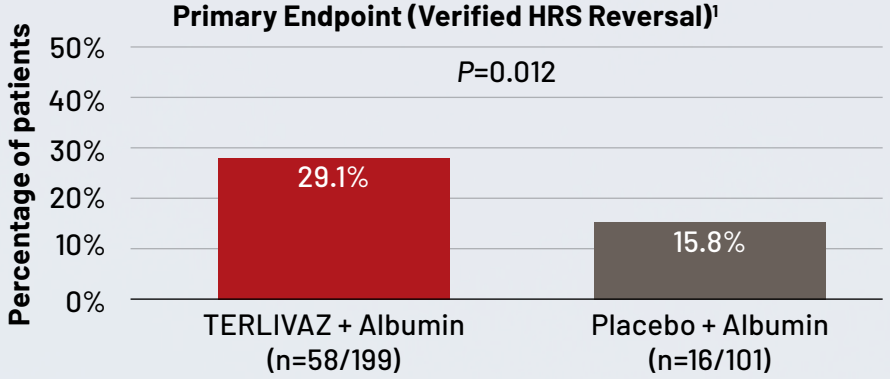
Pivotal Trial
N=300

TERLIVAZ + Albumin (n=199)	2:1 randomization	**Placebo[b] + Albumin** (n=101)

[a] Adults with liver cirrhosis, ascites, and a diagnosis of HRS with a rapidly progressive reduction in renal function (with trajectory for SCr to double within 2 weeks) to a SCr ≥2.25 mg/dL without sustained improvement in renal function 48 hours after withdrawal of diuretics and volume resuscitation/expansion with albumin.
[b] Placebo: mannitol.

TERLIVAZ demonstrated a significantly higher rate of verified HRS reversal, defined as improvement in renal function, avoidance of dialysis, and short-term survival[1]

Primary Endpoint (Verified HRS Reversal)[1]



Multicomponent primary endpoint (verified HRS reversal) was defined as[1]:

- 2 consecutive SCr values **≤1.5 mg/dL (at least 2 hours apart)** by Day 14 or discharge
- Survival without renal replacement therapy (eg, dialysis) for ≥10 days

A multicomponent endpoint was selected to demonstrate a clinically meaningful outcome beyond a surrogate marker of renal function.

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  Manage intravascular volume overload by reducing or discontinuing the administration of albumin and/or other fluids and through judicious use of diuretics. Temporarily interrupt, reduce, or discontinue TERLIVAZ treatment until patient volume status improves. Avoid use in patients with ACLF Grade 3 because they are at significant risk for respiratory failure.

HRS, hepatorenal syndrome; NEJM, New England Journal of Medicine; SCr, serum creatinine.

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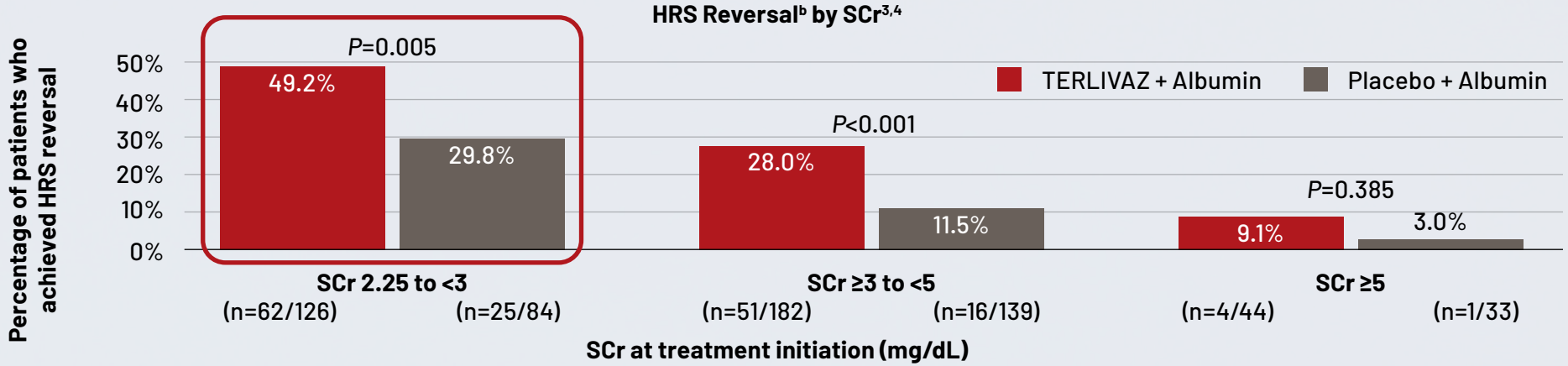
TERLIVAZ® Treatment Earlier in Disease Progression Was Associated With a Higher Rate of HRS Reversal[3,4]

POOLED DATA FROM THREE PHASE 3 TRIALS OF TERLIVAZ: INTEGRATED ITT POPULATION[a]



This pooled analysis includes data from CONFIRM, OT-0401 (N=112), and REVERSE (N=196). OT-0401 and REVERSE are phase 3, prospective, multicenter, randomized, double-blind, placebo-controlled trials with 1:1 randomization that evaluated the efficacy and safety of TERLIVAZ for the treatment of HRS-1.[5,6,c,d]

Limitation of Analysis: HRS reversal is a surrogate endpoint using a single SCr measurement of ≤1.5 mg/dL. Conclusions based on these data may be limited.

Limitation of Use: Patients with SCr >5 mg/dL are unlikely to experience benefit.

[a] The integrated ITT population is the population created from the pooling of the 3 studies. The integrated ITT is defined as all randomized patients. The primary endpoint for the summary of clinical efficacy was incidence of HRS reversal. [b] HRS reversal: the percentage of patients who achieved a decrease in SCr to ≤1.5 mg/dL during treatment without dialysis.[5] [c] Neither OT-0401 nor REVERSE met their primary endpoint. [d] HRS reversal was a secondary endpoint in all 3 trials and was defined as a decrease in SCr to ≤1.5 mg/dL on at least 1 single measurement during treatment without dialysis.[5,6]

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions *(cont)*

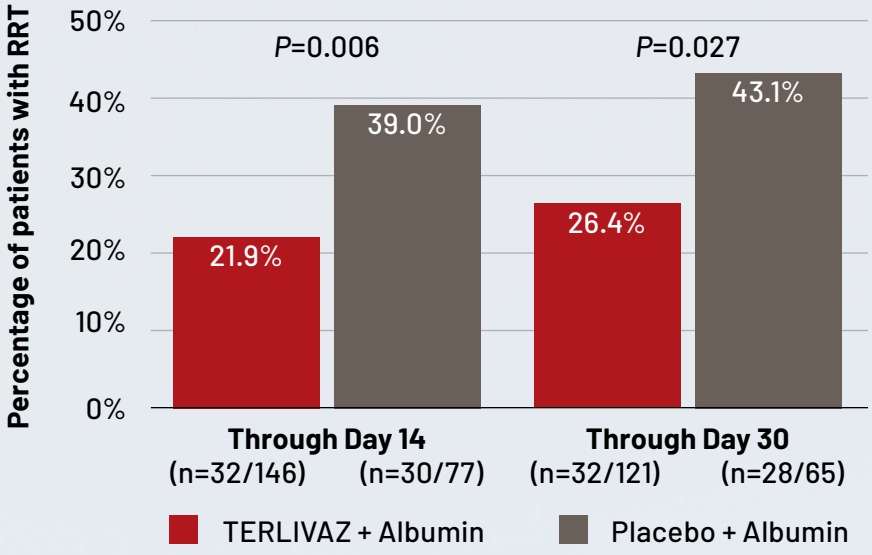
- **Ineligibility for Liver Transplant:** TERLIVAZ-related adverse reactions (respiratory failure, ischemia) may make a patient ineligible for liver transplantation, if listed. For patients with high prioritization for liver transplantation (e.g., MELD ≥35), the benefits of TERLIVAZ may not outweigh its risks.

HRS, hepatorenal syndrome; HRS-1, hepatorenal syndrome type 1; ITT, intention-to-treat; SCr, serum creatinine.

TERLIVAZ® Was Associated With a Lower Incidence of RRT in the CONFIRM Trial[7-9]

POST HOC ANALYSIS OF PRESPECIFIED ENDPOINT

RRT Incidence Through Days 14 and 30[7]

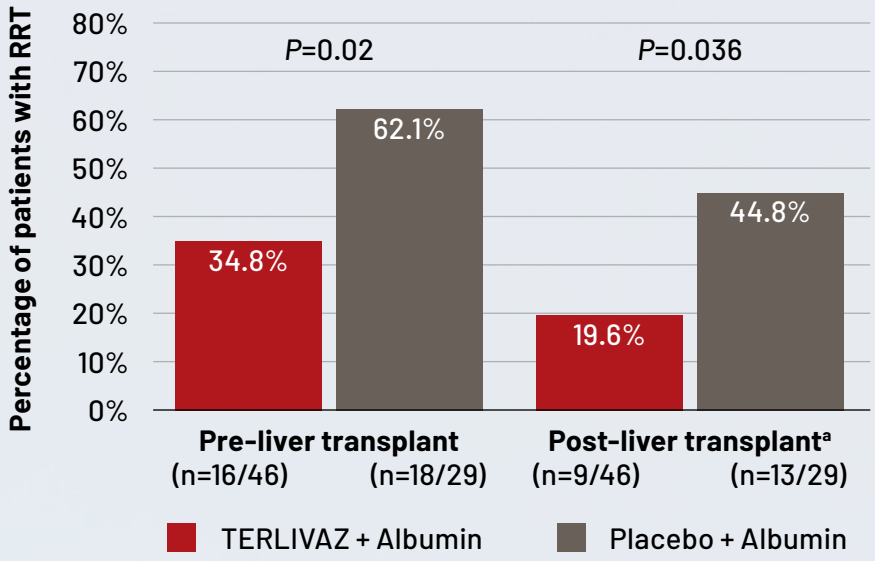


44% relative reduction in RRT at Day 14 and 39% at Day 30 with TERLIVAZ

This post hoc analysis was done to show RRT incidence in patients in the ITT population who were alive through Day 90. The analysis was retrospective and based on a much smaller population than the full randomized population in the CONFIRM trial.

POST HOC ANALYSES OF PRESPECIFIED ENDPOINTS

RRT Incidence Pre- and Post-liver Transplant[8,9]



These post hoc analyses were done to show RRT incidence in patients in the ITT population who received a liver transplant. The analyses were retrospective and based on a much smaller population than the full randomized population in the CONFIRM trial. Those patients who did not receive a transplant were excluded.

[a] 90 days after randomization.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions *(cont)*

- **Ischemic Events:** TERLIVAZ may cause cardiac, cerebrovascular, peripheral, or mesenteric ischemia. Avoid use of TERLIVAZ in patients with a history of severe cardiovascular conditions or cerebrovascular or ischemic disease. Discontinue TERLIVAZ in patients who experience signs or symptoms suggestive of ischemic adverse reactions.

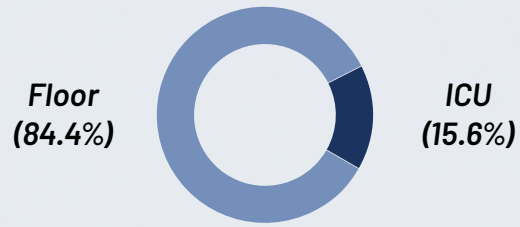
ITT, intention-to-treat; RRT, renal replacement therapy.

In the CONFIRM Trial, TERLIVAZ® Was Used on the Floor and Was Associated With a Reduction in ICU Length of Stay[10]

TERLIVAZ can be used on the floor[1]

- The full Prescribing Information does not include a requirement for cardiac monitoring[a,b]
- TERLIVAZ can be administered through a peripheral IV line; a dedicated central line is not required

Patient treatment location[10,c]

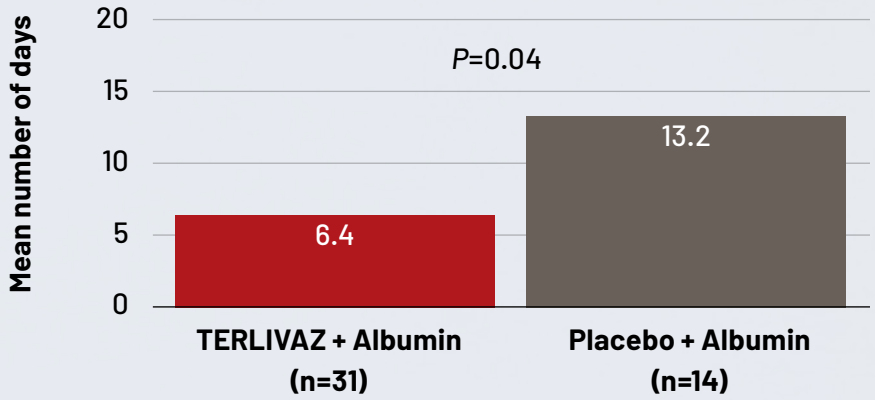


[a] Healthcare professionals are advised to use their own medical judgment in making patient-specific treatment decisions.
[b] The TERLIVAZ Prescribing Information requires continuous pulse oximetry monitoring.
[c] The proportion of patients treated in the ICU was balanced between TERLIVAZ and placebo arms.

POST HOC ANALYSIS

In those admitted to the ICU, TERLIVAZ was associated with a 50% reduction in ICU LOS[10,d,e]

Mean LOS in the ICU[10]



[d] Patient health outcomes were independent of these metrics and results may have varied.
[e] This post hoc analysis was retrospective and based on a much smaller population than the full randomized population in the CONFIRM trial.

IN THE CONFIRM TRIAL ITT POPULATION

TERLIVAZ was associated with a 29% increase in number of patients discharged by Day 14[11]

- 39.2% of TERLIVAZ patients vs 27.7% of placebo patients were discharged by Day 14 (*P*=0.05)*

*Reason for discharge varied among patients and was not necessarily indicative of patient outcomes.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions *(cont)*

- **Embryo-Fetal Toxicity:** TERLIVAZ may cause fetal harm when administered to a pregnant woman. If TERLIVAZ is used during pregnancy, the patient should be informed of the potential risk to the fetus.

ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; LOS, length of stay.

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Adverse Reactions in the CONFIRM Trial

Most Common Adverse Reactions
(reported by ≥4% of patients treated with TERLIVAZ®)[1]

	Patients, n (%)	
	TERLIVAZ + Albumin N=200	**Placebo + Albumin** N=99
Gastrointestinal events		
Abdominal pain	39 (19.5)	6 (6.1)
Nausea	32 (16.0)	10 (10.1)
Diarrhea	26 (13.0)	7 (7.1)
Respiratory events		
Respiratory failure	31 (15.5)	7 (7.1)
Patients intubated, n/total (%)[9,a]	20/31 (64.5)	5/7 (71.4)
Dyspnea	25 (12.5)	5 (5.1)
Fluid overload	17 (8.5)	3 (3.0)
Pleural effusion	11 (5.5)	0 (0.0)
Infections		
Sepsis	11 (5.5)	1 (1.0)
Cardiovascular events		
Bradycardia	10 (5.0)	0 (0.0)
Ischemia-related events[b]	9 (4.5)	0 (0.0)

[a] Not all patients who experienced severe respiratory failure were intubated.
[b] Ischemia-related events include preferred terms: skin discoloration, cyanosis, ischemia, and intestinal ischemia.

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Recommended TERLIVAZ® Dosing Algorithm[1]

After diagnosis and prior to treatment of HRS, assess for:

- Oxygen saturation*
- ACLF grade
- Volume status

Days 1-3

Initial dose: 0.85 mg (1 vial)[a] TERLIVAZ IV every 6 hours
Baseline SCr[b]: Record on Day 1

Day 4

Assess SCr level vs baseline

If SCr has decreased by 30% or more from baseline	If SCr has decreased by less than 30% from baseline	If SCr is at or above baseline value
Continue 0.85 mg[a] TERLIVAZ every 6 hours	TERLIVAZ may be increased to 1.7 mg[a] (2 vials) every 6 hours	Discontinue TERLIVAZ

Continue TERLIVAZ until 24 hours after patient achieves a second consecutive SCr value of ≤1.5 mg/dL at least 2 hours apart or for a maximum of 14 days

Recurrence may occur after treatment discontinuation, and patients may be re-treated if appropriate[12]

*Do not use TERLIVAZ in patients experiencing hypoxia (eg, SpO_2 <90%) until hypoxia resolves.

[a] 0.85 mg terlipressin is equivalent to 1 vial (1 mg). The approved Prescribing Information states the dose of the active moiety, which is terlipressin. Thus, 1 mg terlipressin acetate is equivalent to 0.85 mg terlipressin base, and 2 mg terlipressin acetate is equivalent to 1.7 mg terlipressin base.
[b] Baseline SCr is the last available SCr before initiating treatment.

Amount of TERLIVAZ Received in CONFIRM[9]

Mean duration of treatment

6.2 days in the TERLIVAZ group

6.0 days in the placebo group

Mean total number of doses

20.3 doses in the TERLIVAZ group

19.5 doses in the placebo group

Patients who received a dose increase[c]

57 (28.6%) patients in the TERLIVAZ group

35 (34.7%) patients in the placebo group

Patients re-treated per trial protocol

6 patients in the TERLIVAZ group

0 patients in the placebo group

Patient health outcomes were independent of these metrics, and results may have varied.
[c] At Day 4 per the dosing algorithm, dose increased to 2 vials (1.7 mg).

SELECT IMPORTANT SAFETY INFORMATION

Adverse Reactions

- The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.

ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; IV, intravenous; SCr, serum creatinine; SpO_2, oxygen saturation.

AASLD Guidance and ACG Guidelines Regarding Terlipressin[a]

AASLD 2021[12]*

"The treatment of choice for HRS-AKI[b] is vasoconstrictor drugs in combination with albumin. The **preferred drug is terlipressin**."

ACG 2022[13]

"In hospitalized patients with cirrhosis and HRS[b] without high grade of ACLF or disease, **we suggest terlipressin** (moderate quality, conditional recommendation[c]) or norepinephrine (low quality, conditional recommendation[c]) to improve renal function."

AASLD Guidance for Treatment[12]*

Vasoconstrictor therapy (in combination with albumin)

- Preferred drug: terlipressin[a]
- In settings where terlipressin is not available, norepinephrine should be given
- If neither can be administered, a trial of midodrine in combination with octreotide may be considered
- When treating with vasoconstrictor therapy, albumin should be infused at 1 g/kg on Day 1 of therapy, followed by 40-50 g/day and continued for the duration of therapy
- Other treatment options, such as RRT and transplant, could be considered for certain patients.

[a] TERLIVAZ® (terlipressin) was not evaluated in comparison to other treatments in a head-to-head clinical study.
[b] Definition of kidney injury for HRS: increase in SCr of ≥0.3 mg/dL within 48 hours or percent increase in SCr that is ≥50% of what was known or presumed to have occurred within the prior 7 days.[12,13]
[c] In the ACG guidelines, a strength of recommendation is given as either strong (recommendations) or conditional (suggestions).
*Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, Wong F, Kim WR. Copyright © 2021 American Association for the Study of Liver Diseases. Reproduced with permission of John Wiley & Sons, Inc.

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Select Warnings and Precautions

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AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; HRS-AKI, hepatorenal syndrome-acute kidney injury; RRT, renal replacement therapy; SCr, serum creatinine.

1. TERLIVAZ® (terlipressin). Prescribing Information. Bridgewater, NJ: Mallinckrodt Hospital Products Inc. 2. Wong F et al. *N Engl J Med.* 2021;384(9):818-828. 3. Data on File – Ref-05858. Mallinckrodt Pharmaceuticals. 4. Curry MP et al. *Hepatol Commun.* 2023;7(1):e1307. 5. Sanyal AJ et al. *Gastroenterology.* 2008;134(5):1360-1368. 6. Boyer TD et al. *Gastroenterology.* 2016;150(7):1579-1589.e2. 7. Data on File – Ref-05872. Mallinckrodt Pharmaceuticals. 8. Data on File – Ref-05870. Mallinckrodt Pharmaceuticals. 9. Data on File – Ref-05035. Mallinckrodt Pharmaceuticals. 10. Data on File – Ref-05871. Mallinckrodt Pharmaceuticals. 11. Data on File – Ref-05873. Mallinckrodt Pharmaceuticals. 12. Biggins SW et al. *Hepatology.* 2021;74(2):1014-1048. 13. Bajaj JS et al. *Am J Gastroenterol.* 2022;117(2):225-252.

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