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Original article

Terlipressin in combination with albumin as a therapy for hepatorenal syndrome in patients aged 65 years or older

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ABSTRACT

Introduction and Objectives: Clinical data for older patients with advanced liver disease are limited. This post hoc analysis evaluated the efficacy and safety of terlipressin in patients aged ≥65 years with hepatorenal syndrome using data from 3 Phase III, randomized, placebo-controlled studies (OT-0401, REVERSE, CONFIRM).

Patients and Methods: The pooled population of patients aged ≥65 years (terlipressin, n = 54; placebo, n = 36) was evaluated for hepatorenal syndrome reversal—defined as a serum creatinine level ≤1.5 mg/dL (≤132.6 μmol/L) while receiving terlipressin or placebo, without renal replacement therapy, liver transplantation, or death—and the incidence of renal replacement therapy (RRT). Safety analyses included an assessment of adverse events.

Results: Hepatorenal syndrome reversal was almost 2-times higher in terlipressin-treated patients compared with patients who received placebo (31.5% vs 16.7%; P = 0.143). Among surviving patients, the need for RRT was significantly reduced in the terlipressin group, with an almost 3-times lower incidence of RRT versus the placebo group (Day 90: 25.0% vs 70.6%; P = 0.005). Among 23 liver-transplant-listed patients, significantly fewer patients in the terlipressin versus placebo group needed RRT by Days 30 and 60 (P = 0.027 each). Fewer patients in the terlipressin group needed RRT post-transplant (P = 0.011). More terlipressin-treated patients who were listed for and received a liver transplant were alive and RRT-free by Day 90. No new safety signals were revealed in the older subpopulation compared with previously published data.

Conclusions: Terlipressin therapy may lead to clinical improvements in highly vulnerable patients aged ≥65 years with hepatorenal syndrome.

Clinical trial numbers: OT-0401, NCT00089570; REVERSE, NCT01143246; CONFIRM, NCT02770716

1. Introduction

Hepatorenal syndrome (HRS) is a potentially reversible kidney function impairment occurring in patients with severe chronic liver disease, particularly advanced cirrhosis, and sometimes during acute liver failure [1,2]. HRS is distinguished into 2 types, which differ in their severity and rate of disease progression [2]. HRS type 1 (HRS-1) is characterized by a rapid deterioration in kidney function and, as it meets the modern criteria of acute kidney injury (AKI) outlined by Kidney Disease Improving Global Outcomes (KDIGO), it is now also known as HRS-AKI [1]. HRS type 2 is now referred to as the non-AKI form of HRS (HRS-NAKI), which is characterized by a reduction in estimated glomerular filtration rate to <60 mL/min [3,4].

Abbreviations: ACLF, acute-on-chronic liver failure; AE, adverse event; AKI, acute kidney injury; ANOVA, analysis of variance; CONFIRM, a multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (The CONFIRM study); CI, confidence interval; HRS, hepatorenal syndrome; HRS-1, hepatorenal syndrome type 1; HRS-NAKI, non-acute kidney injury hepatorenal syndrome; ICA, International Club of Ascites; ICU, intensive care unit; INR, international normalized ratio; ITT, intent-to-treat; KDIGO, Kidney Disease Improving Global Outcomes; LT, liver transplantation; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; N/E, non-evaluable; OT-0401, a double-blind, randomized, placebo-controlled, multicenter phase 3 study of intravenous terlipressin in patients with hepatorenal syndrome type 1 (The OT-0401 study); REVERSE, a multi-center, randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin (The REVERSE study); RRT, renal replacement therapy; SAS, Statistical Analysis Software; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome; SpO_2, pulse oximetric saturation; WBC, white blood cell

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The pathophysiology of HRS-AKI is related to hemodynamic changes occurring in severe liver disease, characterized by ascites, portal hypertension, and a systemic inflammatory state [1]. In 2015, the International Club of Ascites (ICA) revised the definition of HRS-AKI, which has shifted from using the diagnostic criteria of serum creatinine (SCr) doubling to >2.5 mg/dL (>221 μmol/L) in less than 2 weeks, to detecting dynamic changes in SCr levels from baseline (ie, an increase of ≥0.3 mg/dL [≥26.5 μmol/L] within 48 h or ≥50% from baseline) [2]. This new definition allows for earlier detection and therapeutic intervention [5].

Patients with decompensated cirrhosis and ascites who develop AKI, including the subset of patients with HRS, have a 29%–44% 30-day mortality rate [6], and if left untreated, median survival is a matter of days [7]. For these patients, liver transplantation (LT) is the only definitive treatment [1]. LT outcomes depend on renal function; and the need for renal replacement therapy (RRT) before LT is associated with renal failure after LT and predicts poor clinical outcomes [8]. Patients who achieve HRS reversal with vasopressor therapy alone (ie, without RRT) experience good outcomes following LT, similar to patients without HRS who receive a transplant [9]. In patients with HRS, the need for RRT after LT is a profound risk factor for chronic dependency on RRT [4]. Therefore, a pharmacological intervention that reduces the need for RRT in patients with HRS, before and after LT, may be clinically beneficial.

Approximately one-quarter of patients with HRS are older than 65 years [10]. Older patients with HRS have an especially dire prognosis and high LT-wait-list mortality rates across all categories of Model for End-Stage Liver Disease (MELD) score [11,12]. Older patients who receive a transplant tend to have higher post-LT morbidity and mortality rates than younger patients because of an increased chronic kidney disease risk and an increased risk of post-LT complications related to immunosuppressive therapy use, cardiovascular disease, malignancy, and metabolic bone disease, which are common in older individuals [11,12]. Therefore, a comprehensive evaluation of elderly patients before LT is required [13].

Pharmacological therapy that improves kidney function and reverses HRS may serve as a bridge to LT, or improve patient outcomes when LT is not feasible [14]. Terlipressin, a synthetic vasopressin analog is the first vasoconstrictor approved by the US Food and Drug Administration and is indicated to improve kidney function in adult patients with HRS with a rapid reduction in kidney function [15]. Terlipressin is recommended for the treatment of HRS-AKI by the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the European Association for the Study of the Liver guidelines [3,6,16].

The efficacy of terlipressin therapy in adult patients (≥18 years) with HRS-AKI is supported by 3 placebo-controlled Phase III studies [17–19]. The OT-0401 study (NCT00089570, *N* = 112) demonstrated higher rates of HRS reversal (ie, initial and confirmatory SCr measurements of ≤1.6 mg/dL [≤141.4 μmol/L) with terlipressin compared to placebo (33.9% vs 12.5%, *P* = 0.008) [17]. The REVERSE study (NCT01143246, *N* = 196) demonstrated numerically higher rates of confirmed HRS reversal (ie, initial and confirmatory SCr measurements of ≤1.5 mg/dL (≤132.6 μmol/L) without intervening RRT or LT) with terlipressin compared with placebo, as well as a significant reduction in SCr levels and a correlation between decreased SCr levels and patient survival [18]. In CONFIRM (NCT02770716), the largest Phase III randomized, placebo-controlled study in patients with HRS to date (*N* = 300), terlipressin was more effective than placebo in improving renal function with higher rates of verified HRS reversal (ie, 2 consecutive SCr measurements of ≤1.5 mg/dL (≤132.6 μmol/L) and survival without RRT; 32% vs 17%, *P* = 0.006) and HRS reversal (ie, SCr of ≤1.5 mg/dL (≤132.6 μmol/L) during the first 14 days; 39% vs 18%, *P* < 0.001) in patients with decompensated cirrhosis and HRS-AKI [19]. The need for RRT was numerically smaller for patients in the terlipressin group compared with the placebo group in the CONFIRM study [19]. However, in CONFIRM, terlipressin therapy was associated with serious adverse events (AEs), including respiratory failure, which occurred in 10% of patients in the terlipressin group versus 3% in the placebo group; corresponding rates of acute respiratory failure were 4% and 2%, respectively [19].

Clinical studies in patients aged ≥65 years with advanced liver disease are limited; therefore, an unmet need exists for data specific to this highly vulnerable population of patients with HRS-AKI [11,20]. This post hoc analysis aimed to evaluate the efficacy and safety of terlipressin in patients aged ≥65 years with HRS-AKI using pooled data from the 3 North American-centric Phase III randomized, placebo-controlled studies (ie, OT-0401, NCT00089570 [18]; REVERSE, NCT01143246 [17]; and CONFIRM, NCT02770716 [19]).

2. Patients and Methods

2.1. Study design and patient population

This post hoc analysis collated data from the intent-to-treat (ITT) and safety subpopulations of patients aged ≥65 years from the OT-0401 [17], REVERSE [18], and CONFIRM [19] studies. The designs for each trial have been previously reported [17–19]. In brief, eligible patients aged ≥18 years with cirrhosis, ascites, and HRS-AKI were enrolled. HRS-AKI was defined as a rapidly progressive worsening in renal function with a SCr level of ≥2.25 mg/dL (≥198.9 μmol/L; CONFIRM) [19] or ≥2.5 mg/dL (≥221 μmol/L; OT-0401; REVERSE) [17,18] and a doubling in the SCr level ≤14 days before randomization. Patients with a sustained improvement in renal function (ie, *a* >20% decrease in SCr or a SCr level of ≤2.25 mg/dL (≤198.9 μmol/L) for at least 48 h after diuretic withdrawal and plasma volume expansion with albumin) were excluded [17–19].

Patients were randomly assigned to receive either terlipressin acetate 1 mg (equivalent to 0.85 mg terlipressin free base) or placebo by bolus intravenous injection every 6 h for ≤14 days; the dose could be increased to 2 mg every 6 h if the SCr level decreased by <30% from baseline after ≥10 doses; concomitant daily albumin was strongly recommended [17–19]. Study treatment (terlipressin or placebo) continued until 24 h after a SCr of ≤1.5 mg/dL (≤132.6 μmol/L) had been obtained, up to 14 days (or a maximum of 15 days if SCr first reached 1.5 mg/dL (132.6 μmol/L) on Day 14). The active study period extended from the initiation of study treatment through Day 14 (or 15 as permitted, per above) or discharge from the hospital for any reason, whichever occurred first.

The pooled safety population included all randomly assigned patients from the OT-0401 [17], REVERSE [18], and CONFIRM [19] studies who received ≥1 dose of the study drug (terlipressin or placebo); the subpopulation of patients aged ≥65 years was examined in this analysis.

2.2. Outcomes

The effect of terlipressin on clinical outcomes in the pooled ITT population was evaluated for HRS reversal and RRT incidence during treatment, during observation through Day 90, and after LT; the duration of hospital stay was also assessed. HRS reversal was defined as any SCr level of ≤1.5 mg/dL (≤132.6 μmol/L) while receiving terlipressin or placebo, without RRT, LT, or death [17–19]. The cumulative frequency of RRT was calculated as the number of times a patient received RRT; more than 1 RRT per day was possible. Duration assessments for overall survival and survival without RRT were calculated from the starting point—defined as the day of randomization for CONFIRM and REVERSE, and the day of the first dose for OT-0401—until the predetermined end date (ie, up to Day 30, 60, or 90).

Safety analyses were based on the pooled safety population and included AEs, permanent withdrawal of the study drug due to AEs, and serious AEs reported in ≥3% of patients.

2.3. Statistical analysis

Binary and categorical data were compared using Fisher's exact test. For numerical data, analysis of variance (ANOVA) and Kruskal-Wallis tests were used to generate *P* values following testing for normality. Univariate and multivariate logistic regression analyses were used to evaluate associations between HRS reversal and baseline covariates, including categorical variables (ie, alcoholic hepatitis [present or not present], baseline mean arterial pressure [MAP] <65 mm Hg [yes or no]) and numerical values (ie, baseline SCr, baseline MELD score). Overall survival was analyzed using a 2-sample log-rank test. All statistical tests were 2-sided with a final significance level of 0.05. Statistical analyses were performed using Statistical Analysis Software (SAS®) version 9.4 (Cary, NC, USA).

2.4. Ethical statement

This post hoc analysis uses data previously generated during the Phase III studies which were conducted in compliance with the International Council for harmonisation Good Clinical Practice guidelines, originating from 1975 Declaration of Helsinki. The protocols were approved by a research ethics board at each participating institution; and written informed consent was obtained from all patients [17–19].

3. Results

3.1. Patients

The combined ITT population of patients aged ≥65 years in the 3 studies (*n* = 90) included 54 patients in the terlipressin group and 36 patients in the placebo group. In CONFIRM, 1 patient who was randomly assigned to the placebo group inadvertently received 1 dose of terlipressin (instead of placebo); therefore, for the ITT population, this patient is counted in the placebo group (pooled ITT population, subgroup aged ≥65 years: terlipressin, *n* = 54; placebo, *n* = 36); however, due to the drug received, the patient was assigned to the terlipressin group for the safety analysis (pooled safety population, subgroup aged ≥65 years: terlipressin, *n* = 55; placebo, *n* = 35).

Baseline demographic and clinical characteristics were typical of patients with HRS-AKI and advanced liver disease and were generally comparable between the terlipressin and placebo groups (Table 1). However, more patients in the terlipressin group versus the placebo group had alcoholic hepatitis, baseline MAP <70 mm Hg, or systemic inflammatory response syndrome (SIRS) (*P* = 0.032). Patients in the terlipressin group also had a lower mean MELD score (28.4 vs 31.4, *P* = 0.027) and a lower mean SCr level at study entry compared with those in the placebo group (3.4 mg/dL [300.6 μmol/L] vs 3.8 mg/dL [335.9 μmol/L], *P* = 0.048).

3.2. Clinical outcomes

HRS reversal was observed in 17/54 (31.5%) patients in the terlipressin group versus 6/36 (16.7%) patients in the placebo group (*P* = 0.143). Univariate logistic regression analyses of baseline factors associated with HRS reversal are presented in Table 2. In the terlipressin group, lower baseline MELD score, prior midodrine and octreotide use, and lower baseline international normalized ratio (INR) were associated with HRS reversal (odds ratio [OR] [95% CI] = 0.87 [0.77–0.98], *P* = 0.021; OR [95% CI] = 5.34 [1.45–19.65], *P* = 0.012; and OR [95% CI] = 0.17 [0.03–0.88], *P* = 0.035, respectively). However, association with baseline SCr level was not statistically significant (OR [95% CI] = 0.62 [0.31–1.26], *P* = 0.187). In the placebo group, HRS reversal was associated with a lower baseline SCr level (OR [95% CI] = 0.13 [0.02–0.80], *P* = 0.028); baseline MAP <70 mm Hg

Table 1
Baseline demographics and clinical characteristics of patients aged ≥65 years (intent-to-treat population).

Characteristic	Terlipressin (*n* = 54)	Placebo (*n* = 36)	*P* value[a]
Age (years), mean (SD)	68.5 (3.1)	69.2 (3.8)	0.374
Sex, n (%)			
Male	24 (44.4)	19 (52.8)	0.438
Female	30 (55.6)	17 (47.2)	0.438
Race, n (%)			
American Indian or Alaskan Native	0	1 (2.8)	0.400
Asian	1 (1.9)	0	1.000
Black or African American	1 (1.9)	2 (5.6)	0.561
White	52 (96.3)	32 (88.9)	0.213
Alcoholic hepatitis, n (%)			
Present	6 (11.1)	4 (11.1)	1.000
Not present	48 (88.9)	32 (88.9)	1.000
Prior infection[b], n (%)	0	2 (5.6)	0.157
Prior midodrine and octreotide, n (%)	27 (50.0)	20 (55.6)	0.605
Received prior albumin, n (%)	54 (100.0)	35 (97.2)	0.400
Prior albumin amount (g), n	51	31	
Mean (SD)	318.7 (185.1)	320.2 (181.8)	0.973
SIRS subgroup, n/N (%)[c]	16/48 (33.3)	7/27 (25.9)	0.504
MAP (mm Hg), mean (SD)	75.7 (11.9)	77.3 (9.87)	0.509
MAP <65 mm Hg, n (%)	11 (20.4)	4 (11.1)	0.387
MAP <70 mm Hg, n (%)	20 (37.0)	7 (19.4)	0.074
Alcoholic hepatitis, baseline MAP <70 mm Hg, or SIRS	34 (63.0)	14 (38.9)	0.025
INR, n	51	35	
Mean (SD)	1.9 (0.7)	2.1 (1.0)	0.199
ACLF grade, n (%)			
1	40 (74.1)	21 (58.3)	0.117
2	10 (18.5)	11 (30.6)	0.186
3	4 (7.4)	4 (11.1)	0.709
CLIF-SOFA score, n	36	27	
Mean (SD)	8.8 (2.3)	9.2 (2.4)	0.565
MELD score, n	50	33	
Mean (SD)	28.4 (6.2)	31.4 (5.6)	0.030
Child-Pugh score, mean (SD)	9.5 (2.1)	10.1 (2.0)	0.134
Child-Pugh score, n (%)			
Class A [5–6]	2 (3.7)	0	0.515
Class B [7–9]	24 (44.4)	15 (41.7)	0.794
Class C [10–15]	28 (51.9)	21 (58.3)	0.545
Bilirubin, n	53	36	
Mean (SD), mg/dL	5.4 (6.2)	9.2 (12.3)	0.509
Mean (SD), mmol/L	0.1 (0.11)	0.2 (0.21)	0.509
BUN, n	50	34	
Mean (SD), mg/dL	70.6 (27.0)	78.8 (31.2)	0.336
Mean (SD), mmol/L	25.2 (9.63)	28.2 (11.16)	0.336
SCr at study entry			
Mean (SD), mg/dL	3.4 (1.0)	3.8 (1.1)	0.043
Mean (SD), μmol/L	298.2 (87.89)	338.9 (97.57)	0.043

[a] For continuous variables, *P* values were calculated with an analysis-of-variance or Kruskal-Wallis test, following testing for normality. For categorical variables, *P* values were calculated via a Chi-square or Fisher's Exact test.

[b] Prior infection includes events 14 days before randomization of spontaneous bacterial peritonitis, urinary tract infection, pneumonia, and other for REVERSE and CONFIRM. Prior infection as selected from medical history terms by medical review for OT-0401.

[c] Percentage of SIRS subgroup is calculated based on the subgroup of patients aged ≥65 years from the pooled CONFIRM and REVERSE intent-to-treat population; the total numbers of patients examined were: terlipressin, *n* = 48; placebo, *n* = 27. Results from OT-0401 were excluded because it did not collect SIRS subgroup information.

ACLF, acute-on-chronic liver failure; BUN, blood urea nitrogen; CLIF-SOFA, chronic liver failure-sepsis organ failure assessment; CONFIRM, a multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (The CONFIRM Study); INR, international normalized ratio (prothrombin time); MAP, mean arterial pressure; MELD, Model of End-Stage Liver Disease; n, number of patients in the treatment group; OT-0401, a double-blind, randomized, placebo-controlled, multicenter phase 3 study of intravenous terlipressin in patients with hepatorenal syndrome type 1 (The OT-0401 study); REVERSE, a multi-center, randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin (The REVERSE study); SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Table 2
Univariate logistic regression analysis to determine the association between baseline characteristics with hepatorenal syndrome reversal in patients aged ≥65 years (intent-to-treat).

Baseline parameter	Terlipressin			Placebo		
	n	Odds ratio (95% CI)	*P* value	n	Odds ratio (95% CI)	*P* value
Alcoholic hepatitis	54	1.10 (0.18–6.68)	0.918	36	1.80 (0.15–20.99)	0.639
Baseline serum creatinine	54	0.62 (0.31–1.26)	0.187	36	0.13 (0.02–0.80)	0.028
Male sex	54	0.82 (0.26–2.63)	0.743	36	0.88 (0.15–5.05)	0.881
Race group (White vs non-White)	54	N/E (0–N/E)	0.982	35	0.37 (0.03–4.90)	0.451
Baseline MELD score	50	0.87 (0.77–0.98)	0.021	33	0.96 (0.82–1.13)	0.617
Baseline Child Pugh score	54	0.79 (0.59–1.07)	0.128	36	1.12 (0.72–1.74)	0.620
Baseline MAP	54	0.99 (0.94–1.04)	0.634	36	0.91 (0.81–1.02)	0.116
Baseline MAP <65 mm Hg	54	0.78 (0.18–3.39)	0.737	36	7.00 (0.76–64.61)	0.086
Baseline MAP <70 mm Hg	54	1.29 (0.40–4.20)	0.670	36	6.50 (0.96–44.14)	0.055
Baseline serum sodium	54	1.01 (0.92–1.10)	0.870	36	1.02 (0.87–1.19)	0.856
Baseline total bilirubin	53	0.90 (0.78–1.04)	0.167	36	1.00 (0.93–1.07)	0.935
No precipitating factors for HRS[a]	54	0.99 (0.30–3.30)	0.991	36	1.00 (0.17–5.77)	N/E
Prior midodrine and octreotide	54	5.34 (1.45–19.65)	0.012	36	0.77 (0.13–4.43)	0.765
Baseline INR	51	0.17 (0.03–0.88)	0.035	35	0.88 (0.30–2.56)	0.815
SIRS subgroup	48	1.16 (0.31–4.30)	0.822	27	N/E (0–N/E)	0.959
Alcoholic hepatitis, baseline MAP <70 mm Hg, or SIRS	54	1.12 (0.34–3.69)	0.857	36	1.73 (0.30–10.08)	0.544
Baseline ACLF grade 0–2 vs 3	54	N/E (0–N/E)	0.975	36	0.56 (0.05–6.48)	0.639
Baseline WBC count	46	0.94 (0.76–1.16)	0.554	27	1.20 (0.82–1.75)	0.357
Baseline serum albumin	52	1.35 (0.64–2.82)	0.429	35	0.51 (0.15–1.82)	0.301
Baseline SpO_2	34	1.36 (0.98–1.89)	0.065	17	0.94 (0.49–1.80)	0.845

Baseline parameters include either categorical values (ie, alcoholic hepatitis, male sex, race group, baseline MAP <65 mmHg, baseline MAP <70 mmHg, no precipitating factors for HRS, prior midodrine and octreotide, SIRS subgroup, alcoholic hepatitis, baseline MAP <70 mmHg, or SIRS, baseline ACLF grade 0–2 vs 3) or numerical values (ie, baseline serum creatinine, baseline MELD score, baseline Child Pugh score, baseline MAP, baseline serum sodium, baseline total bilirubin, baseline INR, baseline WBC, baseline serum albumin, baseline SpO_2).

[a] Precipitating factors for HRS consisted of infection, gastrointestinal bleeding, large volume paracentesis, diuretic treatment, and other (most frequently progression of cirrhosis and alcoholic hepatitis).

ACLF, acute-on-chronic liver failure; CI, confidence interval; HRS, hepatorenal syndrome; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; n, number of patients in the baseline characteristic; N/E, non-evaluable; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome; SpO_2, pulse oximetric saturation; WBC, white blood cell.

had a strong trend for an association with HRS reversal (OR [95% CI] = 6.50 [0.96–44.14], *P* = 0.055).

In the multivariate logistic regression with stepwise selection, baseline INR and prior midodrine and octreotide use were independent predictors of HRS reversal in the terlipressin group (OR [95%CI] = 0.19 [0.04–0.99], *P* = 0.048 and OR [95%CI] = 4.63 [1.15–18.59], *P* = 0.031, respectively). The proportion of patients who achieved HRS reversal in the current study and who had received prior midodrine and octreotide administration was 76.5% in the terlipressin group and 66.7% in the placebo group (*P* = 0.632). Since baseline SCr was the only significant variable in the placebo group in the univariate analysis, a multivariate model was not tested.

Overall survival through Day 90 was similar in both study groups in the pooled ITT population (*P* = 0.538); 30/54 (55.6%) patients in the terlipressin group and 19/36 (52.8%) patients in the placebo group died through the observation period (≤90 days). No difference in transplant-free survival between study groups was observed. Overall survival in patients who received a transplant was also similar in the 2 study groups (*P* = 0.361); no patients in the terlipressin group and 1 patient in the placebo group died through the observation period.

Among surviving patients at each post-treatment time point examined, approximately one third as many in the terlipressin group needed RRT compared with those receiving placebo and differences were statistically significant (Fig. 1): by the end of the study (Day 90), 12/27 (70.6%) patients in the placebo group versus 6/24 (25.0%) patients in the terlipressin group received RRT (*P* = 0.005).

Information on patient listings for LT status was collected only in CONFIRM and REVERSE. In the pooled subpopulation of patients aged ≥65 years from CONFIRM and REVERSE (terlipressin, *n* = 48; placebo, *n* = 27), 16/48 (33%) patients in the terlipressin group and 7/27 (26%) patients in the placebo group were listed for LT at baseline. LT and mortality status for these patients are summarized in Table 3. In the terlipressin group, 8/16 (50%) patients who were listed for LT received a transplant; all of these patients were alive at the end of the study (ie, Day 90). Of those patients in the terlipressin group who did not receive a transplant, 3/8 (37.5%) were alive at the end of the study, while 5/8 (62.5%) had died. In the placebo group, 7/7 (100%) of the LT-listed patients received a transplant; all of whom were alive at the end of the study.

At the end of treatment, the incidence of RRT was similar between study groups (LT-listed patients: terlipressin, 12.5%; placebo, 14.3%; Fig. 2A). However, through the observation period, significantly fewer patients in the terlipressin group (versus placebo) needed RRT by Day 30 and Day 60 (31.3% vs 85.7%, respectively at each time point;

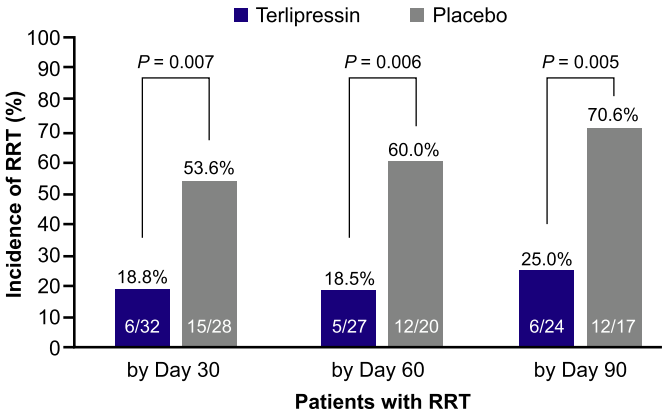

Fig. 1. Incidence of renal replacement therapy among surviving patients aged ≥65 years (pooled intent-to-treat population)[a]

[a]The incidence of RRT among the surviving patients at each time point is represented as n/N, where n is the number of patients receiving RRT, and N is the number of surviving patients at that time point (ie, Day 30, Day 60, or Day 90).

RRT, renal replacement therapy.

Table 3
Transplantation and mortality status for patients ≥65 years of age who were listed for liver transplantation (Pooled intent-to-treat population from CONFIRM[a] and REVERSE[b]).

Mortality status by end of study	Terlipressin (*n* = 16)	Placebo (*n* = 7)
Received a transplant, n	8	7
Alive	8 (100.0)	7 (100.0)
Died	0	0
Did not receive a transplant, n	8	0
Alive	3 (37.5)	0
Died	5 (62.5)	0

Data are presented as n (%).
[a] CONFIRM, a multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (The CONFIRM Study).
[b] REVERSE, a multi-center, randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin (The REVERSE study).

P = 0.027); the mean (standard deviation [SD]) cumulative number of times RRT was received (ie, frequency) through Day 90 was 16.0 (14.30) in the terlipressin group and 32.3 (20.30) in the placebo group (*P* = 0.595). Numerically more terlipressin-treated patients listed for LT were alive and RRT-free by Day 90 compared with the placebo

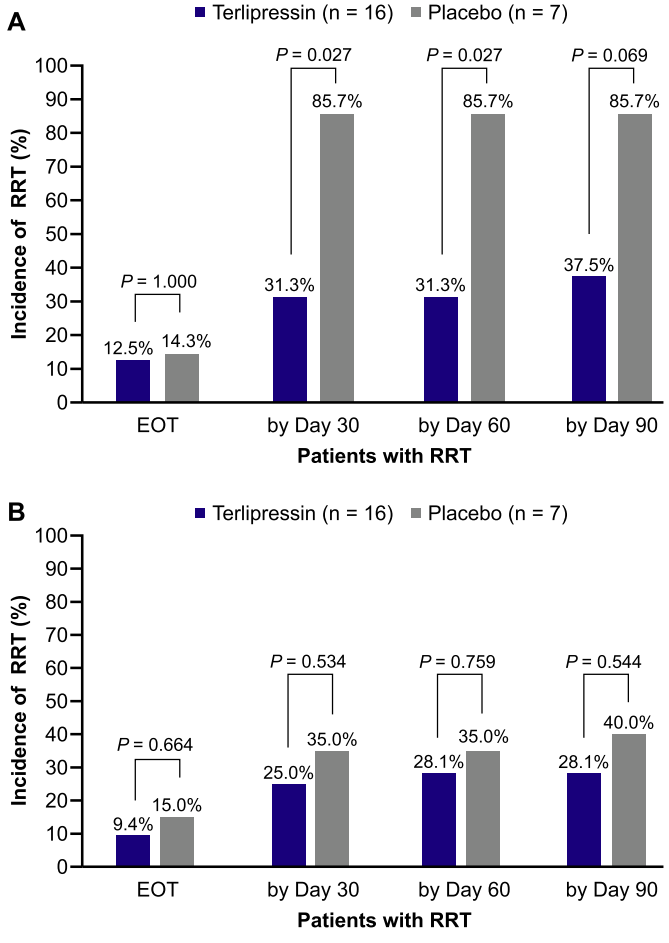

Fig. 2. Incidence of renal replacement therapy by treatment in patients aged ≥65 years for those (A) listed, and (B) not listed for liver transplantation at baseline (pooled intent-to-treat population from CONFIRM[a] and REVERSE[b])
[a]A multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (The CONFIRM Study).
[b]A multi-center, randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin (The REVERSE study).
EOT, end of treatment; RRT, renal replacement therapy.

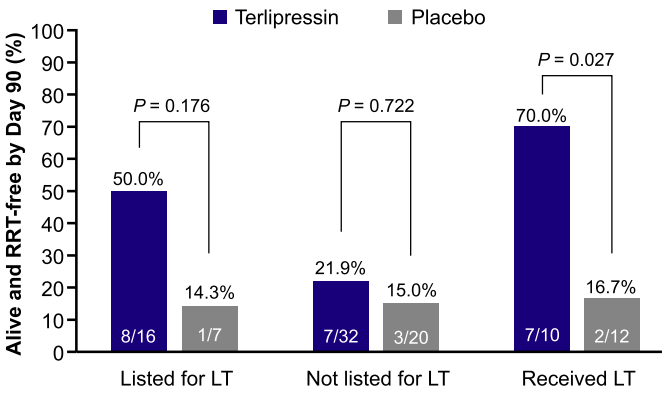

Fig. 3. Renal replacement therapy-free survival by Day 90 in patients aged ≥65 years (pooled intent-to-treat population)[a] by liver transplantation status and treatment
[a]Pooled ITT population of the CONFIRM and REVERSE studies for patients listed and not listed for LT; pooled ITT population of the CONFIRM, OT-0401, and REVERSE studies for patients who received a transplant.
CONFIRM, a multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (The CONFIRM Study); ITT, intent-to-treat; LT, liver transplantation; OT-0401, a double-blind, randomized, placebo-controlled, multicenter phase 3 study of intravenous terlipressin in patients with hepatorenal syndrome type 1 (The OT-0401 study); REVERSE, a multi-center, randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin (The REVERSE study); RRT, renal replacement therapy.

group (50.0% vs 14.3%, *P* = 0.176; Fig. 3). In addition, significantly more transplant recipients in the terlipressin group compared with the placebo group were alive without requiring RRT by Day 90 (70% vs 16.7%, *P* = 0.027; Fig. 3).

For patients not listed for an LT, the need for RRT was not statistically different between treatment groups, (Fig. 2B) and the mean (SD) cumulative frequency of RRT through Day 90 was 2.6 (2.13) in the terlipressin group and 13.4 (17.05) in the placebo group (*P* = 0.595); 21.9% versus 15.0% of patients not listed for an LT in the terlipressin and placebo group, respectively, were alive and RRT-free by Day 90 (Fig. 3).

In the subpopulation of patients aged ≥65 years from the 3 clinical studies, a transplant was received by 10/54 (18.5%) patients in the terlipressin group and by 12/36 (33.3%) patients in the placebo group. Amongst patients who ultimately received a transplant, both the overall incidence of RRT during treatment (terlipressin, 20.0%; placebo, 25.0%; Fig. 4) and the cumulative frequency of RRT throughout the study (ie, both pre- and post-LT) was similar between treatment groups by Day 90 (mean [SD]: terlipressin, 21.3 [24.83]; placebo, 24.1 [20.62]). Whereas, notably after LT, 1 patient in the terlipressin group required RRT (1/10; 10%) compared with 8/12 (66.7%) patients who received RRT post-LT in the placebo group (*P* = 0.011). (Fig. 4).

Furthermore, terlipressin-treated patients had a significantly shorter length of hospital stay compared with patients who received placebo (mean [SD] 21.2 (11.91) days vs 29.6 [19.06] days, *P* = 0.022). Information on the length of intensive care unit (ICU) stay was only available for 4 patients in the terlipressin group and 2 patients in the placebo group; there was a similar duration of ICU stay between the treatment groups (mean [SD] 7.0 [2.94] days and 8.0 [4.24] days, respectively).

3.3. Safety

The frequency of AEs is summarized in Table 4. Most patients aged ≥65 years experienced at least 1 AE: 53/55 (96.4%) in the terlipressin group and 35/35 (100%) in the placebo group. AEs led to treatment discontinuation in 10/55 (18.2%) patients in the terlipressin group versus 0/35 (0%) in the placebo group (Table 4). There were increased incidences of pneumonia and hypotension in terlipressin-treated

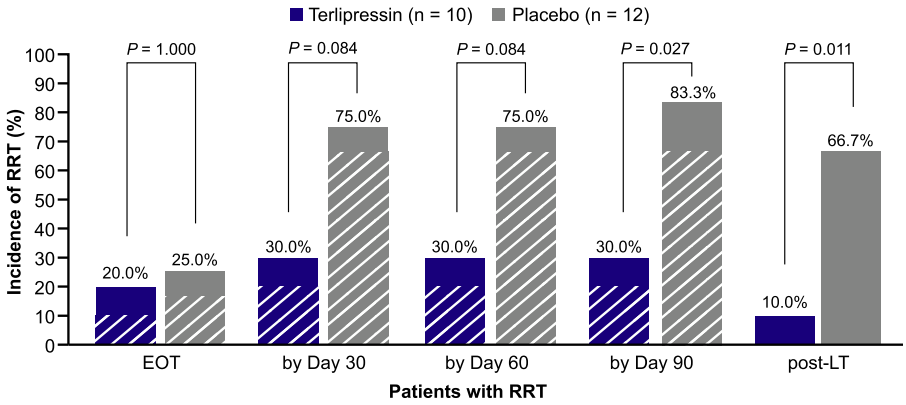

Fig. 4. Incidence of renal replacement therapy in patients aged ≥65 years who received a liver transplant, by treatment (pooled intent-to-treat population)[a]

Hatched bars indicate that RRT occurred before LT, and solid bars indicate that RRT occurred after LT. For the EOT, Day 30, Day 60, and Day 90 timepoints, patients who received RRT both before and after LT were counted as after LT, and RRT ending on the same day as LT was counted as before LT. The post-LT (rightmost) solid bars represent patients who received RRT after LT, regardless of whether RRT was also received pre-LT.

[a]Pooled ITT population of the CONFIRM, OT-0401, and REVERSE studies for patients who received a liver transplant.

CONFIRM, a multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (The CONFIRM Study); EOT, end of treatment; ITT, intent-to-treat; LT, liver transplantation; OT-0401, a double-blind, randomized, placebo-controlled, multicenter phase 3 study of intravenous terlipressin in patients with hepatorenal syndrome type 1 (tThe OT-0401 study); REVERSE, a multi-center, randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin (The REVERSE study); RRT, renal replacement therapy.

patients (each occurred in 9/55 [16.4%]) compared with placebo recipients (0/35 [0%]). In addition, increased incidences of respiratory failure and pleural effusion were observed in terlipressin-treated patients compared with those who received placebo (each, 6/55 [10.9%] vs 0/35 [0%], respectively). Acute respiratory failure occurred in 2/55 (3.6%) terlipressin-treated patients versus 1/35 (2.9%) patients who received placebo (Table 4).

Serious AEs were observed in 41/55 (74.5%) patients in the terlipressin group and in 22/35 (62.9%) patients in the placebo group (Table S1). Serious AEs of respiratory failure and pneumonia were each observed in 5/55 (9.1%) patients treated with terlipressin versus 0/35 (0%) patients in the placebo group; acute respiratory failure was experienced by a similar number of patients in the terlipressin and placebo groups (2/55 [3.6%] vs 1/35 [2.9%]). Of the patients with respiratory failure or acute respiratory failure, 1 terlipressin-treated patient also had pneumonia.

4. Discussion

Data from this post hoc analysis from 3 Phase III clinical studies demonstrate that terlipressin may improve renal function (ie, facilitate HRS reversal) in the overall population of patients aged ≥65 years with HRS-AKI and may reduce the need for RRT in these patients, especially in those listed for LT. Although HRS reversal data did not reach statistical significance—possibly due to the small number of events (n = 23)—the numerical rate of HRS reversal was almost 2 times higher in patients treated with terlipressin compared with placebo (31.5% vs 16.7%). Moreover, similar rates of HRS reversal in response to terlipressin treatment were achieved among patients in this subgroup analysis who were aged ≥65 years (31.5%) compared to historical rates of HRS reversal observed in the overall population in each individual study (CONFIRM, 39.2%; REVERSE, 23.7%; OT-0401, 33.9%) [17–19].

Based on the univariate and multivariate logistic regression analysis, prior midodrine and octreotide use was associated with HRS reversal in the terlipressin group only. The proportion of patients who achieved HRS reversal in the current study and who had received prior midodrine and octreotide administration was slightly greater in the terlipressin group versus the placebo group but was not statistically significant. The effect of prior midodrine and octreotide on the response to terlipressin treatment as a second-line therapy requires further investigation. It is difficult to interpret this statistical finding because the analyses were performed looking at any amount of midodrine and octreotide treatment received by patients (even if only after a few doses) before initiating treatment with terlipressin. In a separate study using the same patient database, three or more days of midodrine and octreotide use was not associated with an improved response on terlipressin [21]. It has been suggested that a delay in treatment initiation in the CONFIRM study might have contributed to a lower response rate and a higher incidence of respiratory failure compared with European studies. Furthermore, it is worth noting that current US and international treatment guidelines recommend terlipressin as a first-line therapy, and the use of midodrine and octreotide treatment only if terlipressin is not available [3,6].

Among surviving patients, the need for RRT was significantly reduced in the terlipressin group at all post-treatment time points evaluated, with almost a 3-times higher incidence of RRT in the placebo group compared with the terlipressin group. RRT is an invasive intervention, especially in patients with HRS-AKI, which is associated with side effects and acute complications such as bleeding, hypotension, increased risk of cerebral edema, and cardiac events [22–24]. Poor outcomes associated with RRT have been previously reported in patients with HRS-AKI and were attributed to hemodynamic instability and coagulopathy [25,26]. Longer pre-LT RRT duration is the strongest independent predictor for nonrecovery of renal function after LT; advanced recipient age is also significantly associated with renal non-recovery [8,27]. Older age was also reported to be an independent negative predictive factor associated with death by 6 months in patients with cirrhosis who initiated RRT, both in LT-listed and non-LT-listed patients [22].

For those patients who were listed for LT at baseline, a difference in the percentage of patients who received a transplant was observed between treatment groups. In the pooled population of patients aged ≥65 years from CONFIRM and REVERSE, 50% of patients who were listed for LT at baseline in the terlipressin group and all patients in the placebo group received a transplant by Day 90. Notably, all patients who received a transplant were alive at the end of the observation period, while 62.5% of those who did not receive a transplant died. One of the limitations of this analysis is that the reasons for not receiving a transplant for LT-listed patients were not recorded.

A reduction in the incidence of RRT in patients listed for LT, and in those after LT, is an important finding. Renal failure and the need for RRT are major risk factors for LT, and pre-LT renal function is the

Table 4
Overview of select adverse events with a frequency of ≥3% in either study group for patients aged ≥65 years (Pooled safety population).

AEs by System Organ Class and Preferred Term	Terlipressin Age ≥65 years (*n* = 55)	Placebo Age ≥65 years (*n* = 35)	*P* value[a]
All reported AEs	53 (96.4)	35 (100.0)	0.519
AEs leading to discontinuation	10 (18.2)	0	0.006
Cardiac disorders	19 (34.5)	7 (20.0)	0.159
Atrial fibrillation	4 (7.3)	6 (17.1)	0.178
Bradycardia	5 (9.1)	0	0.152
Cyanosis	3 (5.5)	0	0.279
Tachycardia	2 (3.6)	2 (5.7)	0.641
Gastrointestinal disorders	29 (52.7)	16 (45.7)	0.666
Abdominal distension	0	2 (5.7)	0.149
Abdominal pain	11 (20.0)	4 (11.4)	0.389
Ascites	2 (3.6)	0	0.519
Diarrhea	14 (25.5)	1 (2.9)	0.007
Gastrointestinal hemorrhage	1 (1.8)	1 (2.9)	1.000
Hemorrhoids	2 (3.6)	0	0.519
Nausea	14 (25.5)	7 (20.0)	0.617
Esophageal varices hemorrhage	3 (5.5)	1 (2.9)	1.000
Vomiting	8 (14.5)	5 (14.3)	1.000
Infections and infestations	19 (34.5)	9 (25.7)	0.485
Peritonitis bacterial	0	2 (5.7)	0.149
Pneumonia	9 (16.4)	0	0.011
Sepsis	3 (5.5)	0	0.279
Septic shock	2 (3.6)	1 (2.9)	1.000
Urinary tract infection	4 (7.3)	2 (5.7)	1.000
Musculoskeletal and connective tissue disorders	9 (16.4)	1 (2.9)	0.082
Pain in extremity	4 (7.3)	0	0.154
Respiratory, thoracic, and mediastinal disorders	25 (45.5)	6 (17.1)	0.007
Acute respiratory failure	2 (3.6)	1 (2.9)	1.000
Cough	0	2 (5.7)	0.149
Dyspnea	8 (14.5)	1 (2.9)	0.146
Epistaxis	1 (1.8)	1 (2.9)	1.000
Fluid overload[b]	5 (9.1)	2 (5.7)	0.701
Hemoptysis	2 (3.6)	0	0.519
Hypoxia	2 (3.6)	0	0.519
Pleural effusion	6 (10.9)	0	0.078
Pulmonary edema	3 (5.5)	0	0.279
Respiratory distress	3 (5.5)	0	0.279
Respiratory failure	6 (10.9)	0	0.078
Tachypnea	2 (3.6)	0	0.519
Wheezing	3 (5.5)	0	0.279
Vascular disorders	17 (30.9)	1 (2.9)	<0.001
Hypotension	9 (16.4)	0	0.011
Shock	3 (5.5)	0	0.279

Data are presented as n (%); patients experiencing multiple adverse events are counted once.
[a] *P* values were calculated via Fisher's Exact or Chi-squared test.
[b] Classified under the Metabolism and nutrition disorders system organ class.
AE, adverse event.

most important predictive factor of renal function and survival after LT [9,28]. Older patients who are listed for LT have high LT-wait-list mortality rates across all categories of MELD score [11]. Importantly, within groups of patients with the same MELD score, higher SCr levels and the need for RRT were previously shown to be associated with decreased LT survival benefit [8].

The data presented herein demonstrate a significant decrease in the need for RRT in LT-listed patients aged ≥65 years who were treated with terlipressin compared with those administered placebo by Days 30 and 60. Notably, terlipressin treatment significantly reduced RRT incidence after LT. Significantly more patients who received a transplant were alive and RRT-free by Day 90 in the terlipressin group compared with placebo, and 1/10 (10%) patients in the terlipressin group and 10/12 (66.7%) patients in the placebo group needed RRT after LT. The reduction in RRT incidence and a shorter mean length of hospital stay by 8.4 days in terlipressin-treated patients may ultimately lead to reductions in both the burden of disease and the cost of treatment.

Recovery of renal function after LT is not universal because of pre-existing comorbidities, unrecognized intrinsic renal disease, unexpected intraoperative events, and immunosuppression after LT, particularly among older patients [1,6]. RRT after LT is associated with chronic dependency on RRT and an increased risk of death in transplant recipients [29]. In contrast, post LT outcomes in patients who experienced HRS reversal with vasopressor therapy alone and who do not require RRT are similar to transplant recipients without HRS [9]. Therefore, by reducing the need for RRT before and after LT, terlipressin may improve LT outcomes in patients ≥65 years of age.

The demonstrated positive efficacy results associated with terlipressin therapy in terms of HRS reversal and RRT incidence did not translate into an improved overall survival benefit in this subpopulation of patients ≥65 years of age. This was not unexpected because HRS-AKI represents only a single aspect of a complex interplay of multiple organ dysfunctions in patients with end-stage liver disease; pharmacological intervention with a vasopressor could be expected to only have a modest effect on overall survival that would be difficult to demonstrate in a relatively small sample size. Notably, out of 22 patients who received a transplant, no patients in the terlipressin group and 1 patient in the placebo group died by Day 90. However, observation beyond 90 days would be needed to allow for long-term conclusions in transplant recipients.

Safety analysis of the pooled subpopulation of patients aged ≥65 years from the 3 Phase III studies did not reveal new signals; however, it confirmed the previously reported risk of developing respiratory failure in patients treated with terlipressin [19]. Careful selection of appropriate candidates and close monitoring of these patients for signs of respiratory distress during treatment may mitigate the safety risks associated with terlipressin therapy.

Limitations of this study include the fact that although data were combined from 3 separate Phase III studies, the relatively small number of patients ≥65 years of age (*n* = 90) and the relatively low frequency of events of interest resulted in a decreased power of analyses; consequently, many effects did not reach statistical significance. Therefore, the results should be interpreted with caution, and additional analyses are warranted. Moreover, certain outcome data were not collected in all 3 studies (eg, LT status data were only recorded in REVERSE and CONFIRM), further reducing the sample size. Additionally, the duration of follow-up did not extend beyond 90 days in CONFIRM and REVERSE [18,19], which precluded evaluation of long-term outcomes. Finally, the Phase III studies were designed before the adoption of the current HRS-AKI criteria proposed by the ICA in 2015, which defined HRS-AKI as a doubling in SCr in 14 days, rather than utilizing a fixed threshold of SCr for diagnosis, allowing for earlier diagnosis and treatment of HRS-AKI [5]. Consequently, the effect of early treatment with terlipressin for HRS-AKI in the older patient population has not been evaluated.

Despite the limitations, these findings are clinically important, especially considering that older patients with HRS-AKI have worse clinical outcomes than younger patients [11,12]. Any therapeutic intervention leading to HRS reversal, and a decreased need for RRT—especially before and after LT—may be clinically beneficial for these extremely sick patients.

5. Conclusions

Post hoc analysis of data from the combined populations from OT-0401, REVERSE, and CONFIRM demonstrate that terlipressin may lead to meaningful improvements in clinical outcomes in the highly vulnerable subpopulation of patients aged ≥65 years with HRS-AKI. Additional studies are warranted to confirm the efficacy results and to further evaluate the safety signals in a larger population of older patients with HRS-AKI.

Author contributions

MAM, SAH, and KJ contributed to the development of the research idea and study design. MAM, AKG-C, MK, PJR, and KJ contributed to data acquisition, analysis, and interpretation. All authors reviewed each draft of the manuscript and approved the final version for submission.

Data availability statement

Discussion of statistical endpoints and analysis are included in the manuscript. Summary aggregate (basic) results (including adverse events information) and the study protocols will be available on clinicaltrials.gov (OT-0401, NCT00089570; REVERSE, NCT01143246; CONFIRM, NCT02770716) when required by regulation. Individual de-identified patient data will not be disclosed. Requests for additional information should be directed to the company at medinfo@mnk.com.

Declaration of interests

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2023.101126.

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