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# Safety and efficacy of continuous infusion terlipressin (BIV201): A phase 2 trial in patients with decompensated cirrhosis and refractory ascites

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## Abstract

Refractory ascites often requires therapeutic paracentesis, which is associated with potential risks and diminished quality of life. Terlipressin is a vasopressin analog that is indicated for i.v. bolus injection for hepatorenal syndrome, with the potential to reduce large-volume ascites and its

**Abbreviations**: AE, adverse event; AESI, adverse event of special interest; AKI, acute kidney injury; AV, atrioventricular; CGI-C, clinical global impression of change; CLDQ, chronic liver disease questionnaire; CTCAE, common terminology criteria for adverse events; EQ-5D-5L, EuroQoL 5 dimension-5 level; FAS, full analysis set; HRS, hepatorenal syndrome; MELD-Na, serum sodium component of MELD; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; PICC, peripherally inserted central catheter; PP, per-protocol; QoL, quality of life; SAE, serious adverse event; SAS, safety analysis set; sCr, serum creatinine; SOC, standard of care; TEAE, treatment-emergent adverse event; TP, therapeutic paracentesis.

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complications. Continuous infusion of terlipressin is associated with fewer adverse effects than bolus dosing. The efficacy and safety of continuous infusion of a novel liquid formulation of terlipressin acetate (BIV201) were evaluated in this open-label phase 2 study. Patients with cirrhosis and refractory ascites were randomly assigned (2:1) to receive two 28-day cycles of continuous infusion BIV201 plus standard of care (SOC) separated by a ≤56-day washout (n = 10), or SOC alone (n = 5). Data analysis was limited by the small sample size and confounded by a potential interaction with gabapentinoids in the BIV201+SOC group. Nonetheless, there were differences in favor of BIV201+SOC versus SOC in the coprimary efficacy endpoints and several quality of life assessments. The beneficial effects of BIV201 on liver complications (mean: 90% CI; BIV201-completers = 2.87: 1.51; 5.46 vs. SOC = 2.38: 1.20; 4.73) and the change in cumulative ascites (mean: 90% CI; BIV201-completers = −10.76: −26.51; 5.00 vs. SOC = −4.99: −21.95; 11.97) were more pronounced versus SOC in the 5 BIV201+SOC patients who completed both treatment cycles. There were also greater improvements in exploratory quality of life assessments and the percent change in therapeutic paracenteses with BIV201+SOC (−27.94 ± 41.80) versus SOC (−16.67 ± 45.64). Despite the high rate of hyponatremia in the BIV201+SOC group (4/10 patients), the safety profile suggested that continuous BIV201 infusion was well tolerated. These findings support further development of BIV201 in confirmatory trials.

**Keywords:** ascites, decompensated cirrhosis, hyponatremia, phase 2 clinical trial, outpatient, terlipressin

## INTRODUCTION

Patients with cirrhosis and ascites suffer from the continuous buildup of ascitic fluid in the abdomen.[1] In some patients, the ascites may become refractory, resisting mobilization by diuretic therapy and sodium restriction.[1] Refractory ascites is associated with poor clinical outcomes, diminished quality of life (QoL), and multiple complications, including spontaneous bacterial peritonitis, acute kidney injury (AKI) including hepatorenal syndrome (HRS-AKI), and hyponatremia.[1–3] The predicted survival rate of patients with refractory ascites may range from ~25% to 50% at 1 year, and expedited referral for liver transplantation is recommended.[2–7]

Standard of care (SOC) for patients with recurrent ascites consists of repeated removal of ascitic fluid through therapeutic paracentesis (TP) or the insertion of a transjugular intrahepatic portosystemic stent shunt in appropriate patients.[1,3] However, TP does not address the underlying pathophysiology and can result in several serious complications.[1,3,8] There are currently no approved pharmacological treatments for refractory ascites.

Terlipressin is a long-acting synthetic analog of vasopressin that mediates vasoconstriction and antidiuretic activity.[9,10] In patients with cirrhosis, terlipressin reduces splanchnic vasodilation associated with portal hypertension, resulting in an increase in effective arterial blood volume.[11] Improved central circulatory volume increases renal perfusion and reduces salt and water retention, thereby decreasing ascites formation via modulation of the renin–angiotensin–aldosterone system.[10]

Terlipressin was recently approved by the U. S. Food and Drug Administration, indicated to improve kidney function in adults with HRS-AKI.[12,13] The administration of terlipressin as intermittent, i.v. bolus injections has been associated with severe adverse events (AEs), including cardiovascular and respiratory complications associated with hypervolemia and redistribution of circulatory volume.[14–17] By contrast, continuous infusion of terlipressin can be a well-tolerated, effective treatment to reduce ascites accumulation and associated symptoms while improving muscle strength, plasma sodium regulation, and QoL.[9,14,18–22] Here, we report the safety, tolerability, and efficacy of continuous infusion terlipressin (BIV201) plus SOC versus SOC alone, administered on an outpatient basis, in adult patients with refractory ascites secondary to decompensated hepatic cirrhosis. The study was terminated early due to the demonstrated efficacy, safety, and tolerability of BIV201, with data suggesting a need to modify the study criteria. The decision to terminate the study was made by the sponsor; it was neither based on a safety concern nor suggested by the Data Safety and Monitoring Board.

# METHODS

## Study design

This exploratory phase 2 study was an open-label, dose titration, randomized, prospective, controlled trial of continuous infusion BIV201 plus SOC (BIV201+SOC) versus SOC alone in patients with cirrhosis and refractory ascites (Figure 1). The study was not designed for hypothesis testing, aiming instead to obtain precise estimates for planning a larger, sufficiently powered efficacy trial. The planned study design included pretreatment, treatment, and 1-year, long-term follow-up periods (Figure 1). The study was discontinued after the last of the enrolled patients completed the 180-day follow-up visit during the treatment period.

During the pretreatment period, patients were monitored for 14–28 days until TP was required; patients were excluded if they did not require a TP. The day of TP was the pretreatment baseline, during which time patients were randomly assigned without matching baseline characteristics (2:1) to BIV201+SOC or SOC. During the treatment period, the BIV201+SOC group received two 28-day cycles of BIV201 that were separated by a washout until relapse (requiring TP) or up to 56 days. In cycle 1, BIV201 was initiated at 3 mg/day and reduced (2 mg/day) or escalated (4 mg/day) based on safety and tolerability. The ending dose of cycle 1 was used throughout cycle 2, unless tolerability warranted de-escalation. This paradigm was designed based on previous studies[18,20] demonstrating that 28 days of continuous BIV201 infusion was sufficient to observe reductions in ascites and need for TP, with some patients (2 of 6) in the phase 2a study experiencing extended control of ascites beyond 28 days of treatment.

Study assessments were performed during each site and home care visit. Site visits for both groups were scheduled on days 1, 14 ± 2 (site or home care visit), and 28 ± 1 of each treatment cycle. Patients randomized to BIV201+SOC had daily nurse visits (except for on-site visit days), and patients randomized to SOC had 2 nurse visits per week. Follow-up assessments occurred 112 ± 14 and 180 ± 14 days after randomization.

## Treatments administered

BIV201 is a novel liquid formulation of terlipressin acetate with long-term stability at room temperature. For the BIV201+SOC group, BIV201 was administered by continuous i.v. infusion through a peripherally inserted central catheter (PICC) line (or midline if specific reason), using a Curlin 6000 CMS continuous therapy ambulatory pump. Daily doses of 2, 3, or 4 mg were achieved by adding 1 or 2 syringes of BIV201 to a 50-mL bag of 0.9% sodium chloride and adjusting the pump's flow rate. SOC generally included a sodium-restricted diet, TP, and medications as clinically indicated (see Supplemental Methods, http://links.lww.com/LVT/A924).

## Patient selection criteria

Adult (> 18 yr) men and nonpregnant women with refractory ascites (diuretic resistant or intractable, see Supplemental Methods, http://links.lww.com/LVT/A924) secondary to decompensated cirrhosis of the liver [due to metabolic dysfunction–associated steatohepatitis,

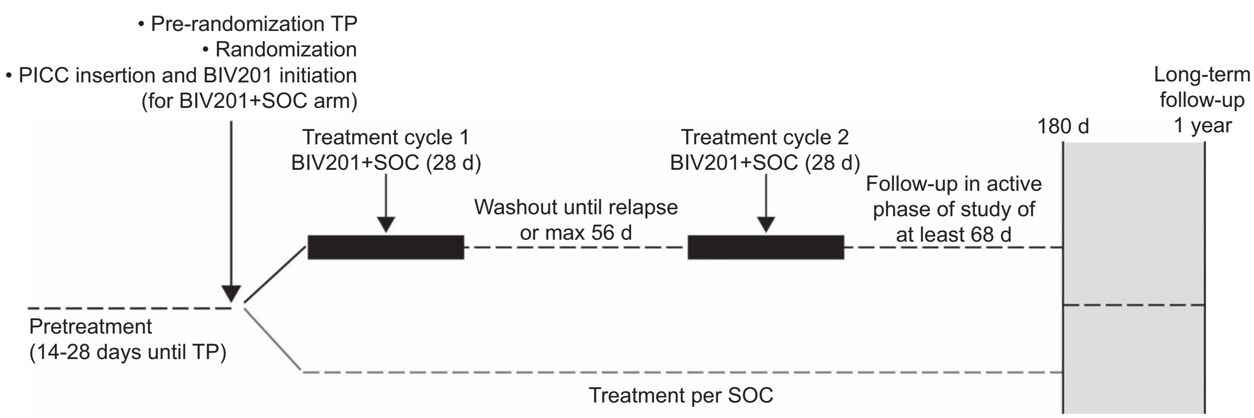


FIGURE 1 Study design. The study was planned to be 1 year but was terminated after the 180-day follow-up. Abbreviations: PD, pharmacodynamic; PICC, peripherally inserted central catheter; SOC, standard of care; TP, therapeutic paracentesis.

(During the study period, the nomenclature and diagnostic criteria for this condition were revised from “nonalcoholic steatohepatitis” to “metabolic dysfunction-associated steatohepatitis.”[23]) alcohol, viral infection, or autoimmune disease] were included in the study. Patients must have had 3 to 9 TPs with known ascitic volumes within 60 days of consent, and stable doses of diuretics for $\geq$10 days prior to consent.

Patients were excluded from the study if they had any of the following key exclusion criteria, among others: ascites with causes other than cirrhosis, urinary sodium excretion $>$100 mmol/day between the day of consent and randomization (see Supplemental Methods, http://links.lww.com/LVT/A924), allergy or hypersensitivity to terlipressin, a cardiovascular disease that was a contraindication to terlipressin, severe organic renal disease, or a renal or liver transplant.

## Endpoints

One of the coprimary efficacy endpoints was the incidence of complications as measured by the annualized complication rate from baseline to 180 days after randomization. Complications of cirrhosis were identified from reported AEs and included $\geq$grade 2 HRS-AKI, gastrointestinal bleeding, HE, hyponatremia, and other blood and electrolyte disorders, and post-paracentesis circulatory dysfunction. A complication was counted if it was considered to be a new event, that is, a recurrence of a previously counted complication that had resolved, and any concurrent complications of different types were counted separately.

The other coprimary efficacy endpoint was the change in cumulative ascites during the first 12 weeks after randomization versus the 12 weeks before treatment. Cumulative ascites over a given period of time was defined as the cumulative weight in kilograms of ascitic fluid drained from 1 or more TPs performed during the period. If a patient did not require a TP by the end of the time interval, the cumulative volume of ascites since randomization was estimated by the sum of the volumes of all TPs (up to the last TP prior to the end of the time interval), plus a linear interpolated volume of the TP immediately after the end of the time interval. The cumulative volume in liters of drained ascitic fluid was converted to weight in kilograms, assuming a density of 1 kg per liter.

Safety endpoints included treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), laboratory tests, vital signs, and electrocardiogram measurements. Hyponatremia was one of several prespecified AESIs and was defined as a decrease in serum sodium of $\geq$5 mmol/L to a serum sodium of $<$130 mmol/L without symptoms (grade 2); or to a serum sodium of $<$125 mmol/L or $<$130 mmol/L with symptoms (grade 3).

Exploratory endpoints included the change in the number of TPs during the first 12 weeks after randomization versus baseline, the time to first TP up to day 112, changes in patient-reported measures of QoL (including the chronic liver disease questionnaire [CLDQ]), changes in renal function as assessed by serum creatinine (sCr), and changes in severity of liver disease as assessed by the serum sodium component of MELD (MELD-Na) score over time, among others.

## Statistical analyses

The full analysis set (FAS) included all randomized patients and was analyzed according to randomized group assignments. The per-protocol (PP) analysis set included all patients in the FAS with no major protocol violations and was analyzed according to actual treatment received. The PP analysis was considered supportive. The safety analysis set (SAS) included all patients who received any investigational product and was analyzed according to the actual treatment received. Due to the small sample size, the only prespecified subgroup analysis that was conducted included comparisons between BIV201+SOC “completers” versus SOC and BIC201+SOC “non-completers” versus SOC. In this subgroup analysis, patients in the BIV201+SOC group were stratified according to the number of BIV201 treatment cycles completed. Statistical analyses (see Supplemental Methods, http://links.lww.com/LVT/A924) were primarily descriptive in nature as the study was not designed for hypothesis testing, aiming instead to obtain precise estimates for the planning of the larger, sufficiently powered efficacy trial. Data were summarized for the FAS, unless stated otherwise, and were assumed to be missing at random from patients who withdrew from the study.

The primary analysis for the effect of BIV201 on the rate of complications was a Poisson regression model that estimated the rate (events per year) of complications and the between-groups incidence rate ratio with a 2-sided 90% CI and $p$ value (see Supplemental Methods, http://links.lww.com/LVT/A924). For the coprimary analysis of the change in cumulative ascites, the treatment difference between BIV201+SOC and SOC was estimated using an ANCOVA model. Results from this analysis included model-estimated mean cumulative ascites during the first 4, 8, and 12 weeks with 90% CIs.

No secondary efficacy endpoints were considered in this exploratory study. Analyses of most exploratory efficacy endpoints followed the same methods as those used for the coprimary efficacy endpoints, as appropriate for continuous and categorical values, and to estimate absolute and percent changes within a given time period after randomization versus baseline. The analysis of the time to first complication (grade $\geq$2) was performed using a Kaplan–Meier method stratified by treatment group for the FAS. Safety data were summarized by treatment group for the SAS.

## Ethics

The study protocol was reviewed and approved by an institutional review board, and in accordance with U.S. Food and Drug Administration regulations. The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki, as well as all national, state, and local laws. Written informed consent was obtained from all patients prior to study enrollment.

# RESULTS

## Patient disposition, demographics, and concomitant medication

Fifteen of the originally planned 30 patients were enrolled in the study, with 10 being randomized to BIV201+SOC and 5 to SOC. Two patients in the BIV201+SOC group discontinued the study due to death (n = 1) and liver transplant (n = 1), and 1 patient in the SOC group discontinued due to death. Fifty percent (n = 5) of the BIV201+SOC group completed both treatment cycles (completers); non-completers discontinued BIV201 during or after cycle 1 (Supplemental Table S1, http://links.lww.com/LVT/A924). On average, BIV201 was administered at a dose of 3.7 mg/day for 36.4 days with a washout of 22.6 days for completers (Supplemental Table S2, http://links.lww.com/LVT/A924).

The BIV201+SOC group comprised both sexes and had a higher mean age compared with the SOC group (Table 1). Patients in the SOC group were diagnosed with decompensated cirrhosis and experienced ascites symptoms at a slightly younger age, and had a longer duration of ascites symptoms, compared with the BIV201+SOC group (Table 1). The ascites was considered intractable in all patients; no patient was treated with the maximum dose of furosemide (160 mg/day) or spironolactone (400 mg/day). While baseline urinary sodium excretion was higher in the SOC group, serum sodium was comparable between treatment groups (Table 1). Ongoing, non-diuretic medications

**TABLE 1** Baseline demographics and disease characteristics

| Characteristic[a] | BIV201+SOC (n = 10) | SOC (n = 5) | Overall (N = 15) |
|---|---|---|---|
| Age, y | 63.1 (7.9) | 57.8 (15.2) | 61.3 (10.6) |
| Sex, n (%) | | | |
| Male | 6 (60.0) | 5 (100.0) | 11 (73.3) |
| Ethnicity, n (%) | | | |
| White | 8 (80.0) | 5 (100.0) | 13 (86.7) |
| Black | 2 (20.0) | 0 (0.0) | 2 (13.3) |
| Body weight, kg | 98.02 (23.37) | 105.82 (45.37) | 100.62 (30.88) |
| Time since cirrhosis diagnosis, mo[b] | 41.0 (45.8) | 24.5 (16.2) | 35.0 (37.5) |
| Age at cirrhosis diagnosis, y | 58.6 (9.7) | 55.6 (15.3) | 57.6 (11.4) |
| Cirrhosis etiology, n (%) | | | |
| MASH | 4 (40.0) | 1 (20.0) | 5 (33.3) |
| Alcoholic | 4 (40.0) | 4 (80.0) | 8 (53.3) |
| Autoimmune | 2 (20.0) | 0 (0.0) | 2 (13.3) |
| Child–Pugh score | 8.7 (1.5) | 8.0 (1.0) | 8.5 (1.4) |
| MELD-Na, mean | 15.00 (5.01) | 13.80 (3.03) | 14.60 (4.42) |
| Age of ascites symptoms onset, y | 61.7 (8.3) | 54.0 (13.7) | 59.1 (10.6) |
| Symptom duration, mo | 22.6 (14.4) | 47.0 (46.2) | 30.8 (29.3) |
| Refractory ascites diagnosis, n (%) | | | |
| Diuretic resistant | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Intractable | 10 (100.0) | 5 (100.0) | 15 (100.0) |
| 24-hour urinary sodium excretion, mmol/24 h | 29.4 (39.95) | 70.3 (83.75) | 40.6 (53.71) |
| Serum sodium, mmol/L | 134.80 (3.58) | 136.20 (4.44) | 135.27 (3.79) |
| Diuretics, n (%) | | | |
| Furosemide | 8 (80.0) | 4 (80.0) | 12 (80.0) |
| Spironolactone | 6 (60.0) | 2 (40.0) | 8 (53.3) |

[a]Data represent the mean (SD), unless otherwise specified.
[b]BIV201+SOC group, n = 7; SOC group, n = 4.
Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; MELD-Na, serum sodium component of MELD; SOC, standard of care.

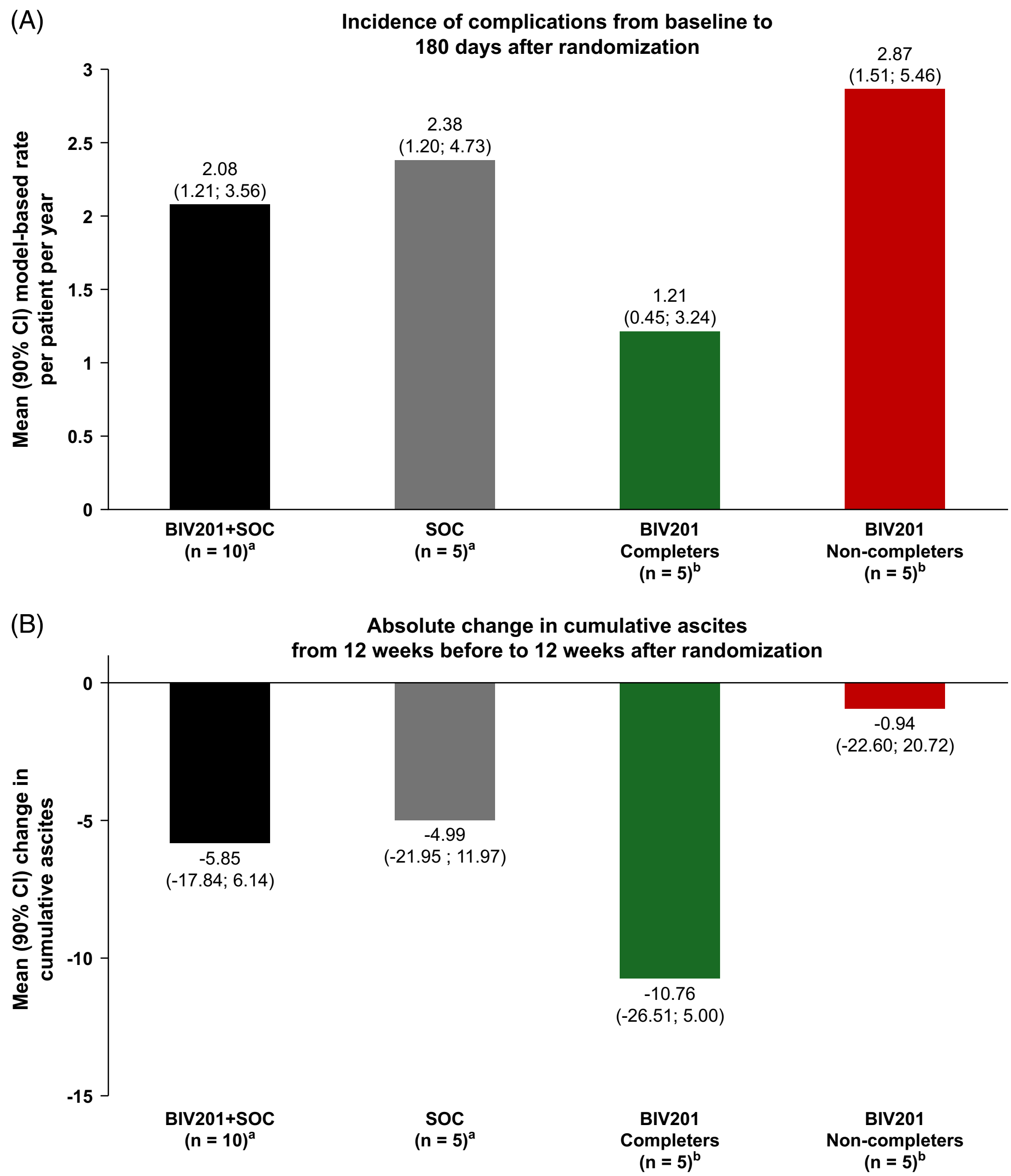


**FIGURE 2** Primary efficacy endpoints. (A) Model-based rate of liver complications per patient per year, and (B) mean absolute change in cumulative ascites from the 12 weeks before to the 12 weeks after randomization. [a]Data were derived from the planned ANCOVA on the full analysis set. [b]Data were derived from separate ad hoc ANCOVAs comparing completers and non-completers against the SOC group. Abbreviation: SOC, standard of care.

included liver therapies and proton pump inhibitors (Supplemental Table S3, http://links.lww.com/LVT/A924), diuretics (including sulfonamides), and aldosterone antagonists (Table 1 and Supplemental Table S4, http://links.lww.com/LVT/A924).

## Positive treatment benefits of BIV201

### Coprimary efficacy endpoints

A numerically lower rate of complications from baseline to 180 days was observed in the BIV201+SOC group versus the SOC group (Figure 2A; Poisson rate ratio = 0.87, 90% CI: 0.37, 2.04; $p = 0.79$). There was a trend toward a greater incidence of hyponatremia and other blood and electrolyte disorders in the BIV201+SOC group, and a trend toward a greater incidence of gastrointestinal bleeding and HE in the SOC group (Supplemental Figure S1, http://links.lww.com/LVT/A924). Ad hoc analyses conducted on the subgroup of completers identified a greater difference favoring the BIV201+SOC completers versus the SOC group (Figure 2A; Poisson rate ratio = 0.52, 90% CI: 0.16, 1.654; $p = 0.35$). By contrast, BIV201+SOC non-completers had a slightly higher rate of complications than

SOC patients (Figure 2A; Poisson rate ratio = 1.24, 90% CI: 0.50, 3.12; $p = 0.70$). However, when events of hyponatremia were omitted from 3 BIV201+SOC patients who were taking gabapentinoids (potential drug–drug interaction, see below), BIV201+SOC completers (Poisson rate ratio = 0.35, 90% CI: 0.09, 1.33; $p = 0.19$) and BIV201+SOC non-completers (Poisson rate ratio = 0.72, 90% CI: 0.25, 2.07; $p = 0.60$) both had lower rates of complications than SOC patients (Supplemental Figure S2, http://links.lww.com/LVT/A924).

The BIV201+SOC group had a slightly larger 12-week change in cumulative ascites versus the SOC group (Figure 2B; mean between-groups difference = −0.86, 90% CI: −20.62, 19.91; $p = 0.94$). The between-groups difference in the change in cumulative ascites was more pronounced in favor of the BIV201 +SOC group during the first 4 (mean difference = −5.45, 90% CI: −9.88, −1.03; $p = 0.048$) and 8 (mean difference = −4.63, 90% CI: −15.86, 6.60; $p = 0.48$) weeks after randomization (Supplemental Tables S5 and S6, http://links.lww.com/LVT/A924). Greater differences between the BIV201+SOC and SOC groups were also observed in completers versus non-completers for both the absolute and percent change in cumulative ascites for all examined time periods (Figure 2B; Supplemental Table S6, http://links.lww.com/LVT/A924).

## Exploratory efficacy endpoints

The absolute mean change in the number of TPs after 12 weeks of treatment was similar between groups (mean ± SD: BIV201+SOC, −1.60 ± 2.50; SOC, −2.00 ± 4.64). However, between-groups comparisons were complicated by the greater number of TPs in the SOC group (9.40 ± 2.41) versus the BIV201+SOC group (6.20 ± 2.74) at baseline. To account for baseline differences, relative changes were quantified. The mean ± SD percent change in TPs after 12 weeks of treatment was greater in the BIV201+SOC group (−27.94 ± 41.80) than in the SOC group (−16.67 ± 45.64). Further, the time to first TP after randomization up to day 112 was prolonged in the BIV201 +SOC group versus the SOC group, and 1 patient in the BIV201+SOC group did not require a TP (Figure 3).

In the BIV201+SOC group, renal function improved during BIV201 treatment cycle 1, as evidenced by a reduction in sCr of ≥ 0.3 mg/dL in 7 patients (70%). sCr rebounded to pretreatment baseline levels after the infusion was stopped. Although sCr improved, MELD-Na did not improve overall in the BIV201+SOC group, largely due to a reduction in serum sodium in 3 patients at some timepoints in those who experienced hyponatremia (see below).

The BIV201+SOC group showed improvements versus the SOC group in several QoL endpoints. The mean total CLDQ score was lower (ie, more severe symptoms) in the BIV201+SOC group versus SOC at baseline but increased to a greater extent (ie, toward less severe symptoms) at most post-treatment assessments (Figure 4A); the mean score of the abdominal symptoms domain of the CLDQ generally increased to a greater extent in the BIV201+SOC group versus the SOC group during the first treatment cycle, but not during the second treatment cycle (Figure 4B). BIV201 +SOC was also associated with a numerical improvement versus SOC in EuroQoL 5 dimension-5 level (EQ-5D-5L), patient global impression of change (PGI-C),

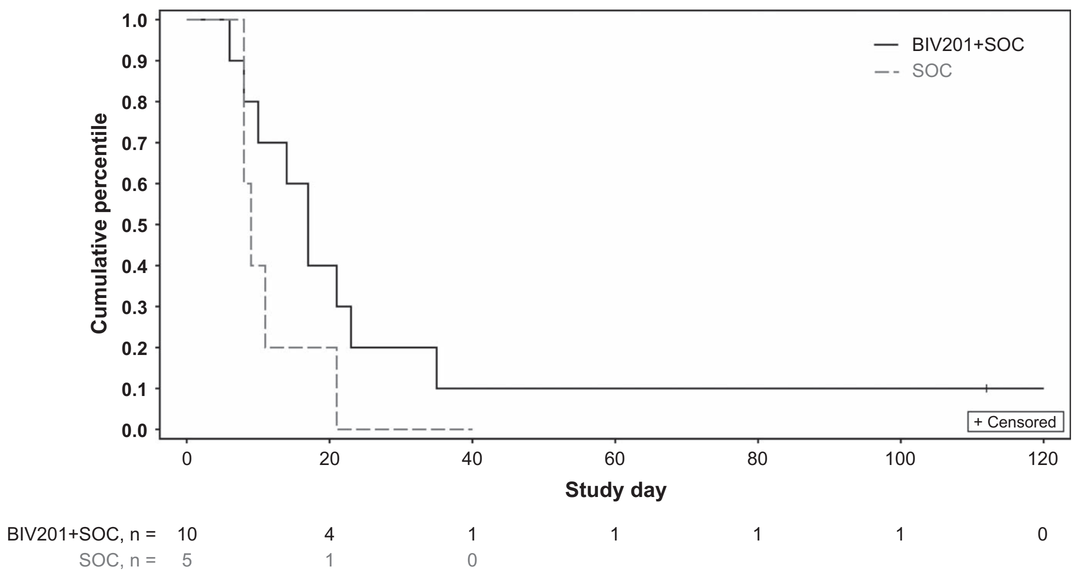


**FIGURE 3** BIV201+SOC prolonged the time to first TP relative to SOC alone. Descriptive analysis of time to first TP up to day 112 was performed using the Kaplan–Meier method stratified by treatment group for the FAS ($p = 0.13$). Abbreviations: FAS, full analysis set; SOC, standard of care; TP, therapeutic paracentesis.

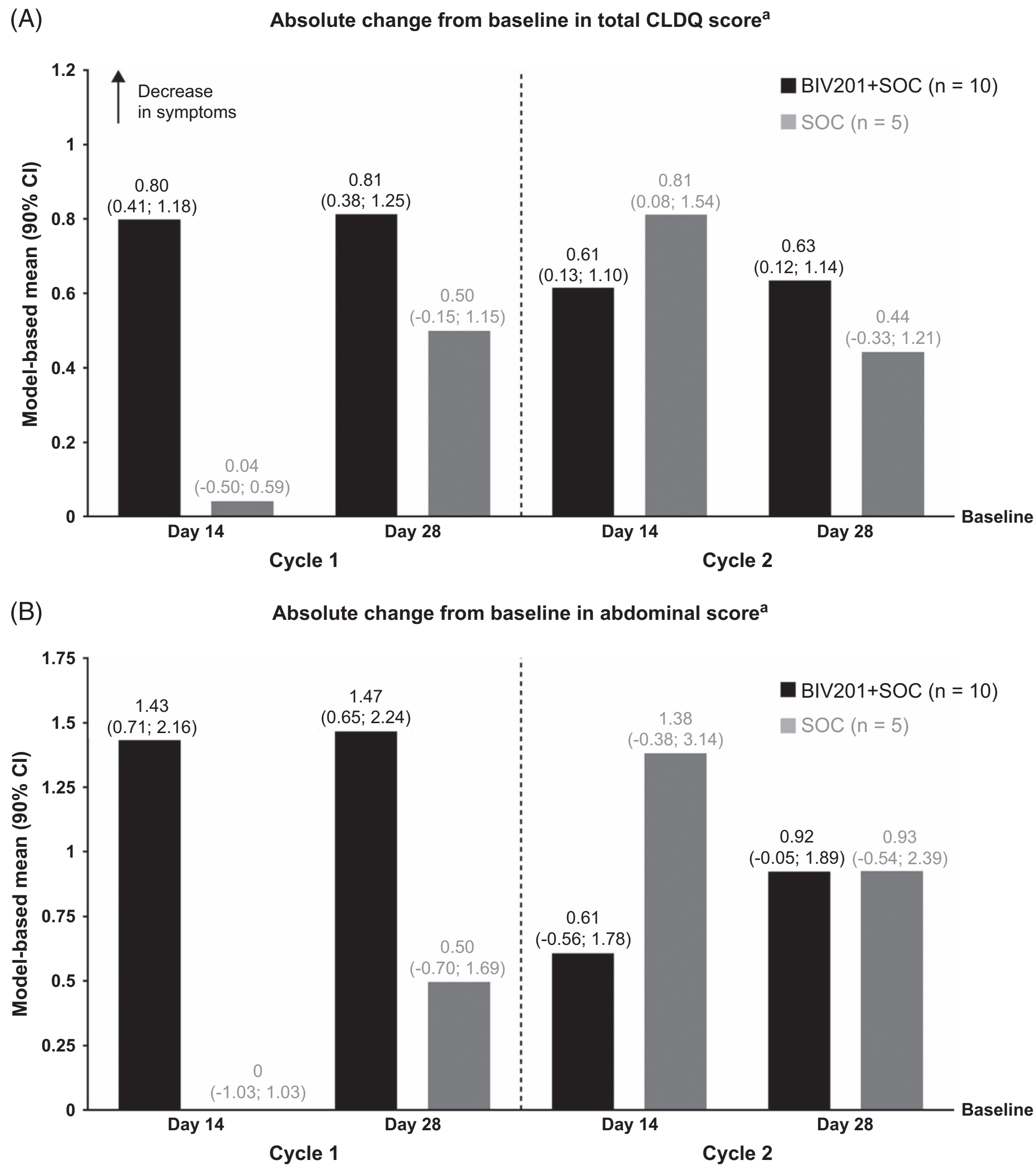


**FIGURE 4** BIV201+SOC was associated with improvements in health status. Absolute change from baseline in (A) total CLDQ scores and (B) abdominal domain subscores of the CLDQ. These data represent model-based means derived from ANCOVA analyses. [a]The CLDQ is scored on a 7-point scale ranging from 1 (all of the time) to 7 (none of the time). A positive change from baseline represents a decrease in symptoms. Abbreviations: CLDQ, chronic liver disease questionnaire; SOC, standard of care.

patient global impression of severity (PGI-S), and clinical global impression of change (CGI-C) scores at the end of cycle 1 (Supplemental Table S7, http://links.lww.com/LVT/A924).

## Tolerability and safety of BIV201

At least 1 TEAE was reported for all patients in both groups (Table 2). The most frequently reported TEAEs in the BIV201+SOC group included pruritus, nausea, abdominal pain, diarrhea, hyponatremia, and muscle spasms, and the most frequently reported TEAEs in the SOC group included asthenia, nausea, vomiting, HE, fatigue, pyrexia, COVID-19, pruritus, and anemia (Supplemental Table S8, http://links.lww.com/LVT/A924). In the BIV201+SOC group, 3 TEAEs were assessed as being related to study treatment, including hyponatremia (in 2 patients) and headache (in 1 patient). Hyponatremia was the most frequently reported grade $\geq 3$ TEAE (reported in 3 patients in the BIV201+SOC group). Nausea was the only grade $\geq 3$ TEAE that was reported in $>1$ patient in the SOC group.

**TABLE 2** Summary of adverse events

| Patients with at least 1 AE | n (%) BIV201 +SOC (n = 10) | SOC (n = 5) | Overall (N = 15) |
|---|---|---|---|
| TEAE | 10 (100.0) | 5 (100.0) | 15 (100.0) |
| Maximum toxicity grade 1 | 0 (0.0) | 1 (20.0) | 1 (6.7) |
| Maximum toxicity grade 2 | 2 (20.0) | 0 (0.0) | 2 (13.3) |
| Maximum toxicity grade 3 | 4 (40.0) | 2 (40.0) | 6 (40.0) |
| Maximum toxicity grade 4 | 3 (30.0) | 1 (20.0) | 4 (26.7) |
| Maximum toxicity grade 5 | 1 (10.0) | 1 (20.0) | 2 (13.3) |
| Study drug–related TEAE | 3 (30.0) | 0 (0.0) | 3 (20.0) |
| SAE | 7 (70.0) | 4 (80.0) | 11 (73.3) |
| TEAE with CTCAE grade ≥3 | 8 (80.0) | 4 (80.0) | 12 (80.0) |
| Study drug–related TEAE with CTCAE grade ≥3 | 2 (20.0) | 0 (0.0) | 2 (13.0) |
| Study drug–related SAE | 1 (10.0) | 0 (0.0) | 1 (6.7) |
| TEAEs that were AESIs | 6 (60.0) | 2 (40.0) | 8 (53.3) |
| SAEs that were AESIs | 3 (30.0) | 1 (20.0) | 4 (26.7) |
| TEAEs leading to discontinuation of the study drug | 4 (40.0) | 0 (0.0) | 4 (26.7) |
| Study drug–related TEAEs leading to discontinuation of the study drug | 2 (20.0) | 0 (0.0) | 2 (13.3) |
| Study procedure–related TEAEs | 1 (10.0) | 1 (20.0) | 2 (13.3) |
| Death | 1 (10.0) | 1 (20.0) | 2 (13.3) |

Abbreviations: AE, adverse event; AESI, AE of special interest; CTCAE, common terminology criteria for AEs; SAE, serious AE; SOC, standard of care; TEAE, treatment-emergent AE.

Both groups had similar rates of SAEs (serious AEs) (Table 2; Supplemental Table S9, http://links.lww.com/LVT/A924). A greater percentage of BIV201+SOC patients had AESIs, as well as SAEs that were AESIs. The only SAE that was reported in >1 patient in either group was hyponatremia, which was reported in 2 patients in the BIV201+SOC group and related to BIV201 treatment in 1 of the 2 patients. Hyponatremia was also the most frequently reported AESI in the BIV201+SOC group. Other AESIs in the BIV201+SOC group included bacterial peritonitis, bacteremia, post-procedural complications, first-degree atrioventricular (AV) block, hypertension, generalized edema, and acute myocardial infarction. The SAE of bacteremia was assessed as related to the study procedure (PICC line infection) and unrelated to BIV201. The patient's PICC line was removed, a single treatment with cefepime (50 mL) was administered, and the line was reinserted 7 days later. No other patients experienced PICC line complications. AESIs in the SOC group included post-procedural complications, cardiovascular disorder, atrial fibrillation, and gastrointestinal hemorrhage (serious).

One patient in each group died due to liver disease during the study. Four patients discontinued BIV201 due to at least 1 TEAE (Supplemental Table S1, http://links.lww.com/LVT/A924); hyponatremia was the most frequently reported TEAE (n = 2) leading to BIV201 discontinuation.

The most frequently reported laboratory values that were clinically significant in the BIV201+SOC group versus the SOC group were elevated serum glucose (5 patients, 50%; vs. 1 patient, 25%) and low serum sodium (4 patients, 40%; vs. 1 patient, 20%). The elevated glucose findings were not considered related to treatment or to hyponatremia. In the BIV201+SOC group, 4 out of the 5 patients with elevated glucose had a medical history of type 2 diabetes mellitus. Two out of these 5 patients experienced elevated glucose levels during BIV201 infusion; these events occurred in patients other than those who experienced hyponatremia. One of those patients was a diabetic with a glucose level of 15.09 mmol/L at screening that decreased to 7.21 mmol/L at baseline, increased to 12.04 to 10.99 mmol/L during infusion, and then ranged from 12.32 to 15.15 mmol/L during washout. The other patient was a non-diabetic with a baseline glucose of 5.05 mmol/L that increased to 7.27 mmol/L on day 9 of treatment. For the SOC group, a clinically significant elevation in glucose (recorded as a TEAE) was reported for 1 of the 2 SOC patients with diabetes, with a baseline glucose of 5.77 mmol/L that increased to 12.98 on day 41.

The low serum sodium laboratory values were consistent with the more frequent reports of hyponatremia in the BIV201+SOC group. A slightly greater mean ± SD change (decrease) from baseline in serum sodium (mmol/L) was observed in the BIV201+SOC group (2.22 ± 7.1) versus the SOC group (0.25 ± 2.1) on day 28. However, the SDs were sufficiently large and the trend was sufficiently inconsistent (ie, the trend was reversed at some timepoints during cycle 2) such that no overall trend in changes from baseline in mean sodium values was apparent over time (Supplemental Table S10, http://links.lww.com/LVT/A924).

Few patients in either group had abnormal vital signs reported as TEAEs; these included hypertension and hypotension in the BIV201+SOC group (each in 1 patient) and tachycardia in the SOC group (1 patient).

## DISCUSSION

In this phase 2, randomized, open-label, controlled study, the efficacy and safety of BIV201+SOC versus SOC alone were evaluated in adult patients with refractory ascites secondary to decompensated liver cirrhosis. Despite the early study termination, limited sample size, and unexpected rate of hyponatremia in the BIV201+SOC group, prespecified subgroup efficacy analyses demonstrated trends toward treatment benefits of continuous infusion of BIV201 plus SOC compared with SOC alone, particularly during treatment with BIV201.

Overall, the incidence of TEAEs, including serious TEAEs, was similar in both groups, and 1 patient in each group died due to underlying liver disease. Hyponatremia and diarrhea were reported in a greater percentage of BIV201+SOC patients than SOC patients. The hyponatremia developed gradually, was asymptomatic, and resolved upon discontinuation of BIV201 in 2 patients. For 1 of those patients, serum sodium continued to drop despite discontinuation of diuretics. This phenomenon was also observed in the phase 2a study[18] and was recently characterized in a pooled analysis across studies.[24] While the administration of terlipressin as an i.v. bolus injection is known to cause hyponatremia, continuous infusion of terlipressin can improve serum sodium levels in patients with refractory ascites.[21,25] Here, the patients in the BIV201+SOC group who experienced hyponatremia reported concomitant use of gabapentinoids, which can lead to water retention and diluted serum sodium concentrations.[8] Thus, we recently proposed that the relatively high rate of hyponatremia in the BIV201+SOC group may have been caused by a pharmacodynamic interaction between terlipressin and gabapentinoids.[24] The exclusion of gabapentinoid use may reduce the incidence of hyponatremia in patients who receive BIV201.

Neither coprimary endpoint achieved a statistically significant between-groups difference in the FAS. These null results may have been partly attributable to the low number of enrolled patients and the discontinuations and shorter treatment durations in the BIV201+SOC patients who developed hyponatremia. Additionally, there were some notable between-groups differences at baseline that may have impacted the study results, such as differences in disease characteristics, number of performed TPs, and monthly ascites accumulation. These baseline differences may have been expected given the small sample size and the dispersion of patient enrollment across sites. Nonetheless, numerical improvements were observed in the BIV201+SOC group versus the SOC group for the primary efficacy endpoints in the subgroup analyses, though these analyses are only considered as supportive.

The annualized incidence of complications from baseline to 180 days was not different between treatment groups in the FAS. However, the incidence of complications in the BIV201+SOC group was driven mainly by the event of hyponatremia, which is believed to have resulted from a drug–drug interaction that accounts for 8 of the 10 events in that group versus only 2 of the 6 events in the SOC group. Further, only half of the BIV201+SOC patients completed both treatment cycles (56 days of BIV201 infusion), which limits the study's ability to determine the effects of this regimen on liver complications over 180 days. Additional studies with larger groups of patients who complete the entire regimen will help to inform on the time course of the benefits of continuous infusion BIV201 on clinical outcomes in patients with recurrent ascites.

In the prespecified subgroup analysis, including only patients who completed both treatment cycles, there was a greater difference in liver complications in favor of the BIV201+SOC group versus the SOC group. A subsequent sensitivity analysis demonstrated a more pronounced effect when events of hyponatremia were omitted from the patients with concomitant gabapentinoid use. Similar results were observed for the 12-week change in cumulative ascites, with only a slight difference favoring the BIV201+SOC group in the FAS that was more robust among completers in the subgroup analysis. Other exploratory endpoints also demonstrated modest differences between groups in favor of BIV201+SOC versus SOC. These included the mean percentage change in the number of TPs, the time to first TP, and several patient-reported measures of QoL, such as the CLDQ. However, the benefit of BIV201 on these exploratory assessments was only observed at certain timepoints. The variability in these assessments over time is challenging to interpret, but may have resulted in part from the small sample size. Notably, feedback from the investigators that was available for 4 of 5 patients who completed both cycles of BIV201 indicated that those patients would have continued treatment with BIV201 had the protocol allowed it.

These results are consistent with previous studies from our group and others demonstrating a clinical benefit of continuous infusion of terlipressin in patients with cirrhosis and uncontrolled ascites.[18,20,22,26] The sustained hemodynamic effects of continuous terlipressin infusion may help preserve renal function in patients with ascites, improving cardiac reserve and reducing the risk of HRS-AKI.[27,28] A recent study found that ~50% of patients with cirrhosis who are managed on an outpatient basis develop complications gradually, with 42% of those patients progressing to acute decompensation.[29] Notably, mortality was higher among those patients than compensated patients, highlighting the need to improve outpatient treatment options and prevent further decompensation. Additional long-term, multicenter studies are needed to determine whether BIV201 may be an appropriate outpatient treatment option for reducing ascites and liver complications, including HRS-AKI, in patients with decompensated cirrhosis.

As noted above, the interpretation of these results is limited by several considerations. First, the study was not sufficiently powered to detect statistically significant between-groups effects. The small sample size was partly a consequence of the study design, which aimed to obtain estimates on which to base a larger and sufficiently powered efficacy trial, and partly due to the premature termination of enrollment after 15 of the planned 30 patients were enrolled. Additionally, only half of the patients in the BIV201+SOC completed 2 full cycles of active treatment, and there were potentially meaningful between-groups differences in disease characteristics at baseline, such as the need for TP. Second, there are potentially confounding factors that were not monitored and could have impacted the study's results, such as adherence to a sodium-restricted diet or alcohol consumption, although patients were excluded from the study if they were judged to have been excessive alcohol drinkers within 12 weeks of enrollment.

Despite these limitations, there were some numerical trends in favor of BIV201+SOC versus SOC in the prespecified subgroup analysis that warrant further investigation into the impact of continuous infusion of BIV201 on clinical outcomes. The observed safety profile suggests that BIV201 was well tolerated, with no new serious risks identified. The design of a new phase 3 study, which evaluates the efficacy and safety of BIV201 and employs a multi-day drug format, will benefit from the information and experiences obtained from this study.

## AUTHOR CONTRIBUTIONS

Jasmohan S. Bajaj, Ethan M. Weinberg, K. Rajender Reddy, Andrew P. Keaveny, David Koch, Paul J. Thuluvath, and Douglas A. Simonetto participated as clinical site investigators, enrolled subjects in the study, and participated in advisory meetings related to the study. Eric S. Orman and Sujit V. Janardhan were clinical site investigators of sites that did not enroll subjects due to the early study termination but participated in advisory meetings and data discussions. Paolo Angeli and Michael K. Porayko were key advisors on study design and ongoing data analysis. Susan Clausen participated in study protocol design and study setup. Jeffrey Zhang conducted statistical analysis for the study. Elisa Dauphinée managed study operations and oversaw data acquisition. Joseph M. Palumbo oversaw study safety, and Penelope Markham, as program and scientific lead, participated in all aspects of the study and manuscript preparation. All authors critically reviewed the manuscript, contributed to revisions, and approved the final submission.

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