Safety and Tolerability of Continuous Infusion Terlipressin (BIV201) in Patients With Decompensated Cirrhosis and Refractory Ascites: A Phase 2, Randomized, Controlled, Open-Label Study

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BACKGROUND

- The development of diuretic-resistant ascites is a serious complication in patients with decompensated cirrhosis and is associated with poor quality of life and high mortality[1,2]
  - The standard of care (SOC) involves transjugular intrahepatic portosystemic shunt (TIPS) or physical removal of ascites via therapeutic paracentesis (TP)[3]
  - Unfortunately, TP only provides temporary relief,[5] lacks disease-modifying effects, and can lead to complications, such as bleeding, renal failure, and CV events[3,4]; TIPS can result in hepatic encephalopathy[5]
- Terlipressin is an analog of vasopressin that suppresses renin-angiotensin-aldosterone system activation, increases renal perfusion and excretion, partly via splanchnic vasoconstriction, and is currently in development to treat refractory ascites[6]
  - Terlipressin administered as an IV bolus injection is indicated for improvement of renal function in adults with HRS[7]; however, studies indicate that terlipressin administered as a continuous IV infusion may have a better safety and tolerability profile[6,8]
  - In a phase 2a, open-label trial, BIV201 (terlipressin IV for continuous infusion) was associated with improved control of refractory ascites during the 28-day treatment period, including decreased requirement for TP and reductions in the volume of ascites removed by TP[6]
- In a recently completed phase 2b trial (NCT04112199), BIV201 plus SOC was associated with significantly reduced ascites accumulation and its associated symptoms compared with SOC alone[9]

OBJECTIVES

- To evaluate the safety and tolerability of BIV201 continuous infusion, along with its therapeutic efficacy on ascites recurrence and clinical complications of decompensated cirrhosis with refractory ascites, during the active treatment period
- Here we report safety outcomes from the phase 2b, randomized trial

METHODS

Study Design

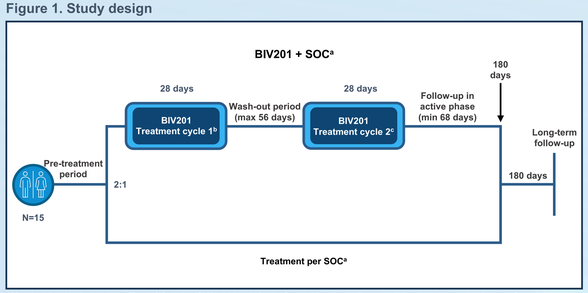
- This was an open-label, phase 2b, dose-titration, controlled study in which adult patients with cirrhosis and refractory ascites were randomized 2:1 to receive either BIV201 in addition to SOC during the intervention period consisting of two 28-day treatment periods separated by a wash-out interval, or SOC alone, followed by a long-term follow-up period of 180 days (**Figure 1**)

Study Population

Key inclusion criteria

- Male or female patients aged >18 years
- Cirrhosis of the liver (NASH, alcohol, viral, and autoimmune)
- Diuretic-resistant or intractable ascites
- Required 3 to 9 TPs in the 6 months prior to consent

Figure 1. Study design



[a]SOC consisted of sustained diuretics and repeat TP per AASLD guidelines; [b]BIV201 administered at 3 mg/day. Dose escalation to 4 mg/day if treatment well tolerated and no pharmacodynamic response. Dose reduction to minimum of 2 mg/day in case of safety concern. [c]Same dose as cycle 1.

Assessments

Primary endpoints (safety)

- Safety and tolerability
- Incidence of the following complications (Grade ≥2) during the 180 days following randomization
  - HRS-AKI
  - Hepatic encephalopathy
  - Gastrointestinal bleeding
  - Post-paracentesis circulatory dysfunction
  - Hyponatremia, acidosis, or hyperkalemia

Exploratory endpoints (safety)

- Incidence of complications during the 84 days following randomization

RESULTS

Baseline characteristics and patient treatment patterns

- Fifteen patients with cirrhosis and refractory ascites were enrolled, and their baseline characteristics are shown in **Table 1**
  - Patients were randomized 2:1 to receive BIV201 + SOC (n=10) or SOC alone (n=5)
  - Both groups were mostly balanced, except patients in the BIV201 group were older, included females, had a higher MELD-Na, and had lower monthly ascites accumulation and plasma renin activity, compared with patients in the SOC alone group
- As shown in **Table 2**, 50% (n=5) of the 10 patients in the BIV201 group completed two 28-day infusion cycles (completers); the other 5 patients discontinued during or at the end of the treatment cycle 1 (non-completers)
  - 70% (n=7) of the 10 patients were escalated to the highest dose (4 mg/day) of BIV201
- 80% (n=4) of the 5 patients in the SOC alone group completed the study
  - 1 patient withdrew consent upon randomization

Table 1. Baseline characteristics[a]

Characteristic	BIV201 + SOC (n=10)	SOC alone (n=5)
Age, y	66 [51-71]	61 [33-73]
Sex, n (%) Male Female	 6 (60) 4 (40)	 5 (100) 0 (0)
Ethnicity, n (%) White Black	 8 (80) 2 (20)	 5 (100) 0 (0)
Etiology, n (%) NASH ALC AI	 4 (40) 4 (40) 2 (20)	 1 (20) 4 (80) 0 (0)
CTP score	8.0 [7-11]	8.0 [7-9]
MELD-Na	16 [11-26]	14.4 [10-18]
SCr, mg/dL	0.93 [0.6-1.8]	1.39 [0.8-1.4]
Albumin, g/dL	2.95 [2.6-3.8]	3.30 [2.3-4.3]
Serum Na, mmol/L	135 [127-140]	136 [129-140]
INR	1.40 [1.06-1.89]	1.2 0[1.00-1.50]
Bilirubin, mg/dL	1.1 [0.7-3.6]	1.4 [0.6-2.2]
12 weeks ascites, L	33.2 [16.0-114.1]	57.2 [38.2-68.5]
Diuretics, n (%) Furosemide Spironolactone	 8 (80) 6 (60)	 4 (80) 2 (40)
PRA, ng/mL/hr	12.42[2.60,34.93]	13.23[1.48,27.45]

[a]Mean [range].

Table 2. BIV201 dose escalation and duration of treatment

Patient number	Highest terlipressin dose (mg/d)	Reason for dose reduction	Total days of BIV201	Washout (days)	Reason for study drug withdrawal
001-001	4	Asymptomatic hyponatremia	21	N/A	Asymptomatic hyponatremia, related
001-004	4	N/A	28	N/A	Inconvenience
002-005	4	N/A	52	23	N/A
004-002	3	N/A	56	56	N/A
004-003	4	N/A	28	N/A	Asymptomatic hyponatremia, related
005-001	4	Strong efficacy	56	6	N/A
005-003	3	N/A	7	N/A	First degree AV block, unrelated
005-005	4	N/A	55	14	N/A
013-001	3	Hyponatremia	55	11	N/A
013-003	4	N/A	21	N/A	Incarcerated hernia, unrelated

Efficacy

- Previously, we showed that treatment with BIV201 plus SOC significantly reduced ascites accumulation, its associated symptoms, measures of the underlying pathophysiology of ascites, patients' monthly TP requirement, and patients' average daily weight, compared with SOC alone[9]

Safety: TEAEs and study drug discontinuation

- During the 6 months after randomization, all patients experienced ≥1 TEAE (**Table 3**); patients randomized to BIV201 experienced a total of 123 TEAEs, of which only 4 were reported as related to the study drug: headache (1) and hyponatremia (3)
- During the 6-month trial period, 11 (73%) of all 15 patients had ≥1 serious TEAE (**Table 4**)
  - The incidence of serious TEAEs was similar in both groups: 7 (70%) of 10 patients randomized to BIV201 plus SOC experienced a total of 19 serious TEAEs, whereas 4 (80%) of 5 patients randomized to SOC only experienced a total of 10 serious TEAEs
- Three of 19 serious TEAEs that occurred in patients randomized to BIV201 plus SOC occurred during BIV201 infusion, including:
  - An episode of hyponatremia (related to study drug) that resolved upon drug cessation
  - An episode of incarcerated hernia considered unrelated to study drug
  - An episode of hypokalemia (unrelated to study drug) in a patient that had neglected to take prescribed potassium tablets

TEAE: hyponatremia

- The most frequent serious TEAE was hyponatremia, which was experienced by 2 patients in the BIV201 plus SOC group and resolved upon discontinuing the study drug (**Tables 2** and **4**; **Figure 2**)
  - A similar resolution of hyponatremia, upon discontinuation of the study drug, was also observed in a patient in the previously conducted phase 2a trial of BIV201 (**Figure 3**)
  - All patients who experienced hyponatremia were taking gabapentenoids (gabapentin or pregabalin)

Table 3. Overall summary of TEAEs

	BIV201 plus SOC (N=10) n (%); m	SOC only (N=5) n (%); m	Total (N=15) n (%); m
Subjects with ≥1 TEAE	10 (100%); 123	5 (100.0%); 58	15 (100%); 181
Subjects with ≥1 related TEAE	3 (30%); 4	0; 0	3 (20%); 4
Subjects with ≥1 TEAE with CTCAE grade ≥3	8 (80%); 23	4 (80.0%); 13	12 (80%); 36
Subjects with ≥1 related TEAE with CTCAE grade ≥3	2 (20%); 2	0; 0	2 (13%); 2
Subjects with ≥1 serious TEAE	7 (70%); 19	4 (80.0%); 10	11 (73%); 29
Subjects with ≥1 serious related TEAE	1 (10%); 1	0; 0	1 (7%); 1
Subjects with ≥1 TEAE leading to discontinuation of study drug	4 (40%); 6	0; 0	4 (27%); 6
Subjects with ≥1 related TEAE leading to discontinuation of study drug	2 (20%)	0; 0	2 (13%)
Subjects with ≥1 TEAE requiring dose adjustment	1 (10%); 1	0; 0	1 (7%); 1
Subjects with TEAE leading to death	1 (10%); 1	1 (20%); 1	2 (13%); 2

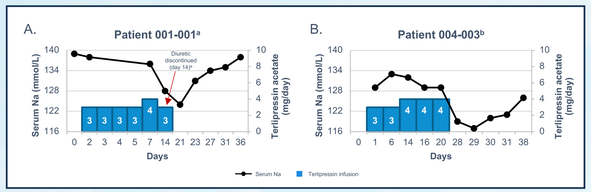
n=number of events; n=number of subjects.

Table 4. Serious TEAEs

	BIV201 plus SOC (N=10) n (%); m	SOC only (N=5) n (%); m	Total (N=15) n (%); m
Any serious event	7 (70%); 19	4 (80%); 10	11 (73%); 29
Hyponatremia	2 (20%); 3	0; 0	2 (13%); 3
Abdominal pain	1 (10%); 1	1 (20%); 1	2 (13%); 2
Disease progression	1 (10%); 1	1 (20%); 1	2 (13%); 2
Acute kidney injury	1 (10%); 1	0; 0	1 (7%); 1
Anemia	1 (10%); 1	0; 0	1 (7%); 1
Bacteremia	1 (10%); 1	0; 0	1 (7%); 1
Blood electrolytes decreased	1 (10%); 1	0; 0	1 (7%); 1
Embolic stroke	1 (10%); 1	0; 0	1 (7%); 1
Generalized edema	1 (10%); 1	0; 0	1 (7%); 1
Hepatic cirrhosis	1 (10%); 1	0; 0	1 (7%); 1
Hepatic encephalopathy	1 (10%); 1	0; 0	1 (7%); 1
Incarcerated hernia	1 (10%); 1	0; 0	1 (7%); 1
Lung cancer metastatic	1 (10%); 1	0; 0	1 (7%); 1
Mental status changes	1 (10%); 1	0; 0	1 (7%); 1
Nonalcoholic fatty liver disease	1 (10%); 1	0; 0	1 (7%); 1
Peritonitis bacterial	1 (10%); 1	0; 0	1 (7%); 1
Serotonin syndrome	1 (10%); 1	0; 0	1 (7%); 1
Back pain	0; 0	1 (20%); 1	1 (7%); 1
Gastrointestinal hemorrhage	0; 0	1 (20%); 2	1 (7%); 2
Nausea	0; 0	1 (20%); 1	1 (7%); 1
Edema genital	0; 0	1 (20%); 1	1 (7%); 1
Small intestinal obstruction	0; 0	1 (20%); 1	1 (7%); 1
Syncope	0; 0	1 (20%); 1	1 (7%); 1
Vomiting	0; 0	1 (20%); 1	1 (7%); 1

n=number of events; n=number of subjects.

Figure 2. Hyponatremia and resolution following drug discontinuation



[a]Patient received 20-mg/day furosemide until day 14. [b]Patient received 40- and 200- mg/day furosemide and spironolactone, respectively, throughout.

Figure 3. Hyponatremia in a patient from the phase 2a trial

[a]Patient received 20-mg/day furosemide until day 5 and 100-mg/day spironolactone until day 8.

Safety: deaths

- There was 1 death in both study groups during the 6-month trial period; both deaths were due to progression of liver cirrhosis
  - One patient from the SOC only group (baseline MELD-Na: 16) passed away 5 months after randomization
  - One patient from the BIV201 plus SOC group (baseline MELD-Na: 26) passed away 75 days after completing two 28-day treatment cycles with BIV201

CONCLUSIONS

- We demonstrated that BIV201 plus SOC was well tolerated and had a favorable safety profile in this patient population
  - Overall, the incidence of all TEAEs, including serious TEAEs, was similar in both treatment groups
- Two patients who received BIV201 experienced hyponatremia that developed gradually, was asymptomatic, and was resolved upon discontinuation of the study drug
  - The same phenomenon was observed in a patient who received BIV201 in the phase 2a study
  - While terlipressin administered as IV bolus is known to cause hyponatremia, it has been reported that terlipressin administered as a continuous infusion can improve serum sodium levels in patients with refractory ascites[10]
  - We noted that all patients who experienced hyponatremia were also taking gabapentenoids, which are known to cause SIADH[11]
  - Based on the consistency, temporality, biological gradient, plausibility, and experimental evidence, the occurrence of hyponatremia may be explained by a pharmacodynamic interaction between terlipressin V2 effects and gabapentenoids
  - The exclusion of gabapentenoid use during the treatment period may reduce the incidence of hyponatremia in patients who receive BIV201
- To date, cumulative safety data from our phase 2a study[6] (6 patients; 131 total days of BIV201 infusion) and phase 2b study (10 patients; 379 total days of BIV201 infusion) further support the safety and tolerability in this population with only 1 SAE related to terlipressin (asymptomatic hyponatremia) in more than 500 days of outpatient treatment with BIV201
- These findings encourage further development and investigation of BIV201 in confirmatory trials for the treatment of diuretic-resistant ascites in patients with decompensated liver cirrhosis

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AASLD, American Association for the Study of Liver Diseases; AI, autoimmune; ALC, alcoholic; AV, atrioventricular block; CGI-C, Clinical Global Impression of Change; CTCAE, Common Terminology Criteria for Adverse Events; CTP, Child-Turcotte-Pugh; CV, cardiovascular; HRS, hepatorenal syndrome; HRS-AKI, hepatorenal syndrome–acute kidney injury; INR, International Normalized Ratio; IV, intravenous; max, maximum; MELD-Na, Model of End-Stage Liver Disease–serum sodium component; min, minimum; Na, sodium; NASH, nonalcoholic steatohepatitis; PRA, plasma renin activity; SAE, serious adverse event; SCr, serum creatinine; SIADH, syndrome of inappropriate diuretic hormone; TEAE, treatment-emergent adverse event; V2, vasopressin receptor 2.

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