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

Jasmohan S. Bajaj[1,2], Ethan M. Weinberg[3], K. Rajender Reddy[3], Andrew P. Keaveny[4], Michael K. Porayko[5], David Koch[6], Paul J. Thuluvath[7,8], Douglas A. Simonetto[9], Paolo Angeli[10], Sujit V. Janardhan[11], Eric S. Orman[12], Sammy Saab[13], Jeffrey Zhang[14,15], Susan Clausen[15], Joseph Palumbo[15], Penelope Markham[15]

[1]Richmond VA Medical Center, Richmond, Virginia, USA; [2]Virginia Commonwealth University, Richmond, Virginia, USA; [3]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [4]Mayo Clinic, Jacksonville, Florida, USA; [5]Vanderbilt University, Nashville, Tennessee, USA; [6]The Medical University of South Carolina, Charleston, South Carolina, USA; [7]Mercy Medical Center, Baltimore, Maryland, USA; [8]University of Maryland School of Medicine, Baltimore, Maryland USA; [9]Mayo Clinic, Rochester, Minnesota, USA; [10]University of Padova, Padua, Italy; [11]Rush University Medical Center, Chicago, Illinois, USA; [12]Indiana University School of Medicine, Indianapolis, Indiana, USA; [13]David Geffen School of Medicine, University of California, Los Angeles, California, USA; [14]Princeton Pharmatech, Princeton, New Jersey, USA; [15]BioVie Inc., Carson City, Nevada, USA

BACKGROUND

- Refractory ascites, ascites that cannot be controlled with an effective dose of diuretics, is a serious complication in patients with decompensated cirrhosis, resulting in a poor quality of life and abysmal survival rates[1-3]
  - Physical removal of ascites via therapeutic paracentesis (TP), a first-line SOC,[4] provides temporary relief,[5] lacks disease-modifying effects, and can lead to complications such as bleeding, infections, renal failure, circulatory dysfunction, and CV events[6,7]
  - There is no FDA-approved pharmacological therapy for refractory ascites and the SOC is inadequate,[1,2,5] hence there is an urgent medical need for a safe and effective treatment for this serious condition
- Terlipressin is an analog of vasopressin that suppresses RAAS activation, increases renal perfusion and excretion, partly via splanchnic vasoconstriction, and is currently in development to treat refractory ascites[1]
  - Terlipressin administered as an IV bolus injection is indicated for improvement of renal function in adults with HRS[8]; however, it has been associated with high rates of serious and treatment-emergent adverse events[1,8,9]
  - Studies indicate that terlipressin administered as a continuous IV infusion (BIV201) may have a better safety and tolerability profile compared to the intermittent IV bolus dose approved for use in HRS[10]
- In a recent open-label, phase 2a trial in cirrhotic patients with refractory ascites, BIV201 was associated with improved control of refractory ascites during the 28-day treatment period, including decreased frequency of LVP and reductions in the volume of ascites removed by LVP[1]
- An ongoing phase 2b, randomized, open-label study is investigating the safety, efficacy, and tolerability of BIV201 in patients with refractory ascites over a duration of 1 year

OBJECTIVES

- To evaluate the therapeutic efficacy of BIV201 continuous infusion on ascites recurrence and clinical complications of decompensated cirrhosis with refractory ascites during the active treatment period
- To assess long-term (180-day) effects on clinical outcomes in patients treated with BIV201 + SOC compared to those receiving SOC alone
- Here we report select efficacy outcomes from an interim data analysis of 15 patients enrolled; safety data will be reported at a later date

METHODS

Study Design

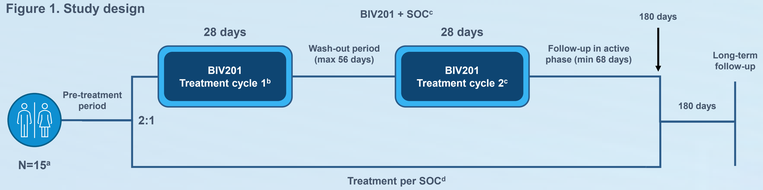
- This was an open-label, phase 2b, dose-titration, controlled study in which adult patients with cirrhosis and refractory ascites were randomized 2:1 to receive either BIV201 during the intervention period consisting of two 28-day treatment periods separated by a wash-out interval, in addition to SOC,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

Study Population

Key inclusion criteria

- Male or female patients age >18 years old
- 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]A total of 30 patients were planned to be enrolled; [b]BIV201 administered at 3 mg/day. Dose escalation to 4 mg/day if treatment well tolerated and no PD response. Dose reduction to minimum of 2 mg/day in case of safety concern; [c]Same dose as cycle 1; [d]SOC consisted of sustained diuretics and repeat TP per AASLD guidelines.

Assessments

Primary endpoints

- Change in cumulative ascites during the first 12 weeks after randomization vs 12 weeks prior to treatment
- 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
- Safety and tolerability

Exploratory endpoints

- Number of TPs during the first 12 weeks after randomization vs 12 weeks prior to treatment
- Incidence of complications during the 84 days following randomization
- Changes in patient-reported dAST (tracks ascites-related symptoms)
- Renal function and severity of liver disease (measured by the MELD-Na score)
- Changes in PGI-C and CGI-C scores
- Changes in PGI-S and health status (measured by CLDQ and EQ-5D-5L)

RESULTS

- 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 slightly lower monthly ascites accumulation and plasma renin activity, compared with patients in the SOC alone group
- 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)
- 80% (n=4) of the 5 patients in the SOC alone group completed the study
  - One patient withdrew consent upon randomization
- After 28 days of treatment, all 10 patients randomized to BIV201 + SOC (completers and non-completers) demonstrated a significant reduction in ascites accumulation compared with 28 days pre-treatment (mean reduction: 34%; *P*=0.004), with 50% (n=5) of these patients experiencing >40% reduction (**Table 2**)
  - In contrast, patients randomized to SOC alone demonstrated a mean increase of 3.4% in ascites accumulation (*P*=0.8), with no patients experiencing a >40% reduction

Table 1. Baseline characteristics

Characteristic	BIV201 + SOC (n=10)	SOC alone (n=5)
Age, y	63.1 [51-71]	57.8 [33-73]
Sex, n (%) Male Female	 7 (70) 3 (30)	 5 (100) 0 (0)
Ethnicity, n (%) White Black	 8 (80) 2 (20)	 5 (100) 0 (0)
CTP score	9.3 [7-12]	8.6 [7-10]
MELD-Na	16 [11-26]	14.4 [10-18]
SCr, mg/dL	1.02 [0.56-1.8]	1.2 [0.8-1.4]
Albumin, g/dL	3.33 [2.3-3.8]	3.16 [2.3-4.3]
Serum Na, mmol/L	135 [127-140]	136 [129-140]
INR	1.4 [1.0-1.9]	1.2 [1.0-1.5]
Bilirubin, mg/dL	1.58 [0.7-3.6]	1.42 [0.6-2.2]
Monthly ascites, L	16.3 [6.2-37.5]	18.9 [14.7-26.9]
Diuretics, n (%) Furosemide Spironolactone	 8 (80) 6 (60)	 4 (80) 3 (60)
PRA, ng/mL/hr	11.7	14.0

Efficacy

- After 12 weeks of treatment, patients who completed both treatment cycles of BIV201 + SOC (n=5; completers) experienced a reduction in ascites accumulation compared with 12 weeks pre-treatment (mean reduction: 43%; *P*=0.06), with 60% (n=3) of these patients demonstrating >40% reduction (**Table 2**)
  - In comparison, patients randomized to SOC alone demonstrated a mean reduction of 12% in ascites accumulation (*P*=0.56)

Table 2. Change in ascites accumulation

Ascites accumulation[a] 4 wk post- vs 4 wk pre-treatment	BIV201 + SOC All patients (n=10)	BIV201 + SOC Completers (n=5)	BIV201 + SOC Non-completers (n=5)	SOC alone (n=5)
Mean, L	11.84 vs 16.36	5.4 vs 11	18.27 vs 21.65	19.18 vs 18.88
LS mean % change (90% CI)	−33.84 (−50.11, −7.56)	−53.11 (−73.2, −32.95)	−14.57 (−34.7, 5.59)	3.0 (−17.1, 23.22)
P value	0.004[b]	0.001[b,c]	0.257	0.806
Ascites accumulation[a] 12 wk post- vs 12 wk pre-treatment	**BIV201 + SOC All patients (n=10)**	**BIV201 + SOC Completers (n=5)**	**BIV201 + SOC Non-completers (n=5)**	**SOC alone (n=5)**
LS mean % change (90% CI)	−19.02 (−44.85, 6.82)	−42.9 (−77.4, −8.47)	4.91 (−29.57, 39.38)	−12.52 (−47.0, 21.95)
P value	0.247	0.063	0.818	0.561

[a]Total ascites volume removed by paracentesis during the period plus, if a paracentesis was not needed at the end of the period, a linear interpolated volume based on next TP; [b]Between treatment groups, difference from SOC alone, *P*≤0.05; [c]Between treatment groups, difference from BIV201 + SOC non-completers, *P*≤0.05.

- In the 12 weeks following randomization, patients who received BIV201 + SOC had a significant reduction in their monthly TP requirement, compared with 12 weeks pre-treatment (mean reduction was 30% [*P*=0.04] and 47% [*P*=0.02] for all patients and completers, respectively; **Table 3**)
  - In comparison, patients who received SOC alone showed a mean reduction of 21% in monthly TP requirement (*P*=0.26)

Table 3. Change in monthly number of TPs

Monthly TPs 12 wk post- vs 12 wk pre-treatment	BIV201 + SOC All patients (n=10)	BIV201 + SOC Completers (n=5)	BIV201 + SOC Non-completers (n=5)	SOC alone (n=5)
Mean	1.53 vs 2.1	0.87 vs 1.53	2.2 vs 2.67	2.47 vs 3.37
LS mean % change (90% CI)	−29.85 (−51.23, −8.47)	−47.0 (−76.28, −17.72)	−12.7 (−41.98, 16.58)	−20.88 (−50.16, 8.4)
P value	0.039	0.021	0.489	0.263

- After 28 days of treatment, patients randomized to BIV201 + SOC demonstrated decreased SCr levels (mean reduction of 0.14 mg/dL [*P*=0.006] and 0.16 mg/dL [*P*=0.019] for all patients and completers, respectively) and lower plasma renin activity (mean reduction of 43% [*P*=0.057] and 61% [*P*=0.048], respectively), compared with baseline (**Table 4**)
  - In comparison, patients who received SOC alone showed a mean reduction of 0.06 mg/dL [*P*=0.315] in SCr levels and a mean increase of 29% [*P*=0.43] in plasma renin activity

Table 4. Changes in pharmacodynamic measures of ascites

Parameter	BIV201 + SOC All patients (n=10)	BIV201 + SOC Completers (n=5)	BIV201 + SOC Non-completers (n=5)	SOC alone (n=5)
SCr, mg/dL Day 28 vs baseline LS Mean change (90% CI) *P* value	 −0.14 (−0.21, −0.07) 0.006	 −0.16 (−0.26, −0.06) 0.019	 −0.11 (−0.21, −0.01) 0.096	 −0.06 (−0.16, 0.04) 0.315
PRA Day 28 vs baseline LS Mean % change (90% CI) *P* value	 −42.6 (−75.23, −10) 0.057	 −60.66 (−104.3, −16.99) 0.048	 −20.0 (−68.88, 28.78) 0.51	 28.39 (−27.9, 84.77) 0.43

- Patients randomized to BIV201 + SOC showed significant improvements in several HRQoL-related exploratory endpoints (**Table 5**)
  - CLDQ score (day 28 vs baseline): mean increase of 0.75 points (*P*=0.009) and 0.44 points (*P*=0.191) in the BIV201 + SOC group (n=10) and the SOC alone group (n=5), respectively
  - CLDQ (abdominal domain) score (day 28 vs baseline): mean increase of 1.52 points (*P*=0.007) and 0.33 points (*P*=0.621) in the BIV201 + SOC group and the SOC alone group, respectively
  - Change in daily ascites symptoms as measured by a novel PRO instrument in development (dAST, daily Ascites Symptoms Tracker) (4 weeks post- vs pre-treatment): mean reduction in dAST score of 37% (*P*<0.001) and 10.5% (*P*=0.382) in the BIV201 + SOC group and the SOC alone group, respectively
- Patients who completed both treatment cycles of BIV201 + SOC experienced a significant reduction in their daily average weight in the first 4 weeks of treatment compared with pre-treatment (mean reduction: 4.22 kg; *P*=0.008) (**Table 5**)
  - In comparison, patients who received SOC alone demonstrated a mean reduction of 1.78 kg (*P*=0.157)
- Feedback available from 4 out of the 5 patients who completed both BIV201 + SOC treatment cycles indicated that all (4/4) patients would have remained on treatment had the protocol allowed it

Table 5. Changes in other treatment outcomes

Parameter	BIV201 + SOC All patients (n=10)	BIV201 + SOC Completers (n=5)	BIV201 + SOC Non-completers (n=5)	SOC alone (n=5)
CLDQ total score Day 28 vs baseline LS Mean % change (90% CI) *P* value	 0.75 (0.36, 1.14) 0.009	 1.13 (0.67, 1.59) 0.002	 0.27 (−0.25, 0.78) 0.414	 0.44 (−0.08, 0.96) 0.191
CLDQ score (abdominal domain) Day 28 vs baseline LS Mean % change (90% CI) *P* value	 1.52 (0.75, 2.28) 0.007	 2.13 (1.17, 3.1) 0.004	 0.75 (−0.33, 1.83) 0.278	 0.33 (−0.74, 1.41) 0.621
Daily dAST score[a] 4 weeks post vs pre-treatment LS Mean % change (90% CI) *P* value	 −37 (−50.93, −23.15) <0.001	 −44.06 (−65.32, −22.81) 0.006	 −31.24 (−50.4, −12.41) 0.020	 −10.52 (−29.58, 8.49) 0.382
CGI-C Day 28 LS Mean (90% CI)	 3.78 (3.22, 4.34)	 4.2 (3.48, 4.92)	 3.25 (2.45, 4.05)	 3 (2.2, 3.8)
Daily weight[a], kg 4 weeks post vs pre-treatment LS Mean change (90% CI) *P* value	 −2.13 (−3.77, −0.5) 0.053	 −4.22 (−6.37, −2.07) 0.008	 −0.47 (−2.39, 1.46) 0.698	 −1.78 (−3.7, 0.15) 0.157

[a]4-week average based on AUC method.

Safety

- Overall, BIV201 was well tolerated with one SAE (asymptomatic hyponatremia) considered related to study drug and no unexpected serious adverse reactions in the >380 days of outpatient BIV201 infusion

CONCLUSIONS

- In this phase 2b, randomized, open-label, controlled study, BIV201 + SOC was associated with the following treatment benefits, compared with those seen with SOC alone:
  - Decreased ascites accumulation during 4 and 12 weeks of treatment vs 4 and 12 weeks prior to treatment, respectively
  - Reduction in the number of monthly TPs required over 12 weeks of treatment vs 12 weeks prior to treatment
  - Improvement in the pharmacodynamic measures underlying the pathophysiology of ascites after 4 weeks of treatment
  - Improvement in the HRQoL-related assessments, particularly in the abdominal domain of the CLDQ, after 4 weeks of treatment
  - Reduction in the average daily weight during 4 weeks of treatment compared with 4 weeks before treatment
- Overall, BIV201 had an acceptable safety profile during >380 days of outpatient treatment
- These findings support further development and investigation of continuous infusion of terlipressin (BIV201) in confirmatory trials for the treatment of refractory ascites in patients with decompensated cirrhosis

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For more information, please contact Penelope Markham (PMarkham@BioViePharma.com)

AASLD, American Association for the Study of Liver Diseases; CGI-C, Clinical Global Impression of Change; CI, confidence interval; CLDQ, Chronic Liver Disease Questionnaire; CTP, Child-Turcotte-Pugh; CV, cardiovascular; EQ-5D-5L, EuroQol 5 dimensions with 5 levels of severity; FDA, Food and Drug Administration; HRQoL, health-related quality of life; HRS, hepatorenal syndrome; HRS-AKI, hepatorenal syndrome–acute kidney injury; INR, International Normalized Ratio; IV, intravenous; LS, least squares; LVP, large volume paracentesis; MELD-Na, Model of End-Stage Liver Disease–serum sodium component; MOA, mechanism of action; Na, sodium; NASH, nonalcoholic steatohepatitis; PD, pharmacodynamics; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PI, principal investigator; PRA, plasma renin activity; PRO, patient reported outcomes; RAAS, Renin-Angiotensin-Aldosterone System; SAE, serious adverse event; SCr, serum creatinine; SOC, standard of care.

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