Efficacy, Safety, and Tolerability of Volixibat in Patients With Intrahepatic Cholestasis of Pregnancy: A Case Series of 4 Patients

Poster 4547-C

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Introduction

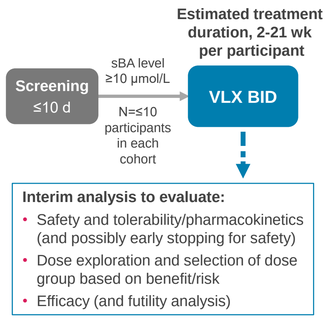
- Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disorder that presents during pregnancy involving cholestatic pruritus, elevated sBA, and increased risk of adverse perinatal outcomes.[1]
- Volixibat (VLX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that interrupts the enterohepatic recirculation.[2]
- To our knowledge, IBAT inhibitors in patients with ICP have not been characterized.

Objective

- To describe 4 patients with ICP treated with open-label volixibat in the OHANA trial (NCT04718961).

Methods

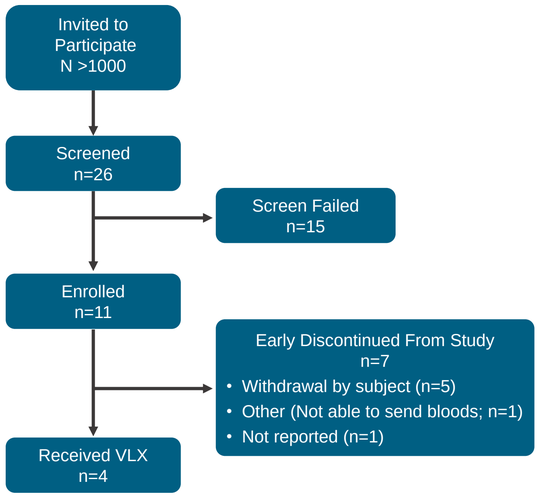
Figure 1. Study Design



- Patients with ICP, sBA level >ULN, and pruritus were treated with open-label volixibat 20 or 80 mg twice daily until delivery.
- Dose modifications were permitted for tolerability.
- Daily pruritus scores (Adult Itch-Reported Outcome [ItchRO] 0-10 scale; 0 = no itch, 10 = worst possible itch), sBA levels, liver enzyme levels, hematology, perinatal outcomes, and treatment-emergent adverse events (TEAEs) were assessed.

Results

Figure 2. Participant Disposition



- >1000 patients were invited to participate; 26 were screened, 11 were enrolled, and 4 patients received volixibat and remained in the study.
  - Small numbers were primarily due to patient reticence for trial participation in pregnancy or not meeting criteria to screen (68.2%), or withdrawal of consent (22.7%).
- Treatment duration was 1-5 weeks.

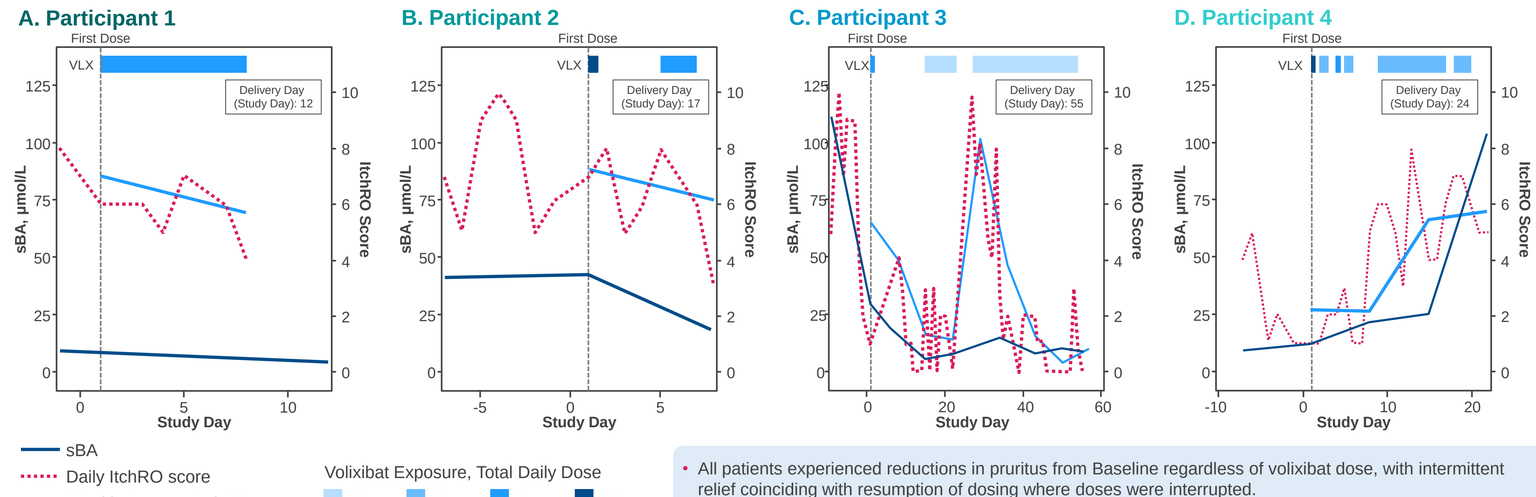
Table 1. Key Baseline Demographics

Participant	1	2	3	4
Age, y	20	25	25	38
Pruritus, ItchRO[a]	7.0	7.3	5.3	2.2
Peak sBA level prior to first dose, µmol/L	9	41	112	9
Initial dose of VLX, mg	40	160	40	160
Treatment duration, wk	1.1	0.6	5.3	2.6

[a]Baseline pruritus is the average weekly ItchRO score prior to maralixibat treatment.

Volixibat Treatment Demonstrated Improvements in Pruritus and sBA Levels in Participants With ICP

Figure 3. Changes in sBA Levels, Weekly Average ItchRO Scores, and Daily ItchRO Scores in 4 Participants (A-D)



- All patients experienced reductions in pruritus from Baseline regardless of volixibat dose, with intermittent relief coinciding with resumption of dosing where doses were interrupted.
- sBA nadir values all reached <6 µmol/L following volixibat treatment.

Table 2. Maternal and Perinatal Outcomes

Participant	1	2	3	4
Pruritus, change from Baseline, ItchRO	-1.3	-2.0	-4.5	3.5
sBA, change from Baseline, µmol/L	-4.2	51.5[a]	-22	-6.6
Gestational age at delivery, wk/d	37/6	35/4	37/1	34/4
Delivery type/mode	Full/V	Preterm/V	Full/C	Preterm/C
Live vs stillbirth	Live	Live	Live	Live
NICU admission	No	Yes	No	Yes/ Respiratory support needed
Maternal complications	Yes[b]	No	No	No
Postpartum hemorrhages	No	No	No	No
ALT change from Baseline to end of treatment, U/L	2	4	44[c]	17

[a]Upon follow-up 3 weeks later, sBA change from Baseline was -38.1 µmol/L.
[b]Preeclampsia with severe features.
[c]Upon follow-up 6 weeks later, ALT change from Baseline was -129 U/L.

Safety Outcomes

- No clinically meaningful changes in liver enzyme levels or hematology parameters were observed after volixibat treatment.
- The most frequent TEAEs were GI in nature.
  - Patient 1 had 1 diarrhea event that was grade 1 severity with a duration of 3 days.
  - Patient 2 had 3 diarrhea events that were grades 2 (2 events, durations 2 and 13 days) and 3 (1 event, duration 2 days).
  - Patient 3 had 1 diarrhea event that was grade 2 (1 event, duration 5 days).
  - Patient 4 had 2 diarrhea events that were grades 2 (1 event, duration 18 days) and 3 (1 event, duration 2 days).
- Three of 4 patients experienced diarrhea and/or abdominal cramping leading to dose reduction, treatment interruption, and/or early discontinuation.
- One patient tolerated treatment until delivery with no dose modifications due to AEs.

Conclusions

- Volixibat demonstrated improvements in pruritus and sBA levels in patients with ICP, signaling proof of concept in this disease.
- This trial had low enrollment numbers, as studies in pregnancy are inherently difficult to enroll.
- Nonetheless, these data warrant further research.

Abbreviations

AE, adverse event; ALT, alanine transaminase; BID, twice daily; C, cesarean; GI, gastrointestinal; IBAT, ileal bile acid transporter; ICP, intrahepatic cholestasis of pregnancy; ItchRO, Itch-Reported Outcome; NICU, neonatal intensive care unit; QD, once daily; sBA, serum bile acid; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; V, vaginal; VLX, volixibat.

Disclosures

CO is a consultant for Mirum Pharmaceuticals Inc. SS and BS have nothing to disclose. EC is a former employee and shareholder of Mirum Pharmaceuticals Inc. DBM, FL, and PV are employees of and shareholders in Mirum Pharmaceuticals Inc. CW is a paid consultant for Mirum Pharmaceuticals Inc., previously advised GSK, and was paid to deliver a webinar by Advanz Pharma.

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References

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