The Safety and Tolerability of ABI-6250, an Orally Administered NTCP Inhibitor in Healthy Participants

P3204

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Background

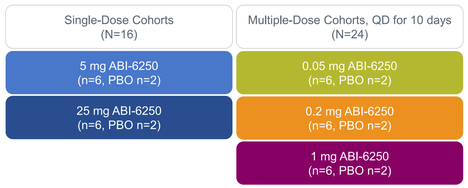
- The sodium taurocholate cotransporting polypeptide (NTCP) mediates the uptake of conjugated bile acid (BA) levels from the portal blood to the liver[1-3]
- NTCP inhibition leads to elevated circulating BAs and decreased intrahepatic BAs[4,5]
- In primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), elevated intrahepatic BA levels lead to inflammation, fibrosis, cirrhosis, and progressive liver disease.[6,7] Reducing intrahepatic BAs via NTCP inhibition may provide a treatment approach for PBC and PSC.[7,8] Bulevirtide (BLV), an NTCP inhibitor administered once daily (QD) by subcutaneous injection, has demonstrated hepatoprotective effects and reductions in intrahepatic BA levels in a mouse model of cholestatic liver disease[4]
- NTCP is utilized by the hepatitis B and D viruses (HBV, HDV) to gain entry into hepatocytes.[9,10] The approval of BLV has validated NTCP inhibition and prevention of viral entry as a treatment strategy for chronic HDV infection[11]
- Orally administered NTCP inhibitors may improve dosing convenience and increase treatment accessibility, particularly in resource-limited settings
- ABI-6250 is an orally administered small-molecule NTCP inhibitor in development for the treatment of PBC, PSC and chronic HDV[12]
- ABI-6250-101 (NCT06740474) is a randomized, blinded, Phase 1a study assessing the safety, pharmacokinetics, and pharmacodynamics of ABI-6250 in healthy participants (HPs; **Figure 1**)

Objective

- To assess the safety and tolerability profile of ABI-6250 following single-dose (SD) and multiple-dose (MD) administration in a Phase 1a study in HPs

Methods

Figure 1. Study Design



Key Inclusion Criteria
- Male or female, aged ≥18 and ≤60 years
- BMI ≥18.0 and <32.0 kg/m^2 (inclusive)
- Female participants with a negative pregnancy test
- In good health (as determined by the investigator)

Key Exclusion Criteria
- Positive for HIV, HBV, HCV, or acute HAV
- Known history of Gilbert's syndrome
- History of illness that may confound the study results
- Persistent alcohol or illicit drug use within 3 years prior to Screening

BMI, body mass index; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PBO, placebo; QD, once daily.

- This study assessed SD and MD ABI-6250 regimens in HPs (**Figure 1**)
- Two SD cohorts and 3 MD cohorts were enrolled, each containing 8 HPs: 6 receiving ABI-6250 and 2 receiving placebo (PBO). The following ABI-6250 dose levels were evaluated:
  - SD: 5 mg and 25 mg
  - MD: 0.05 mg, 0.2 mg, and 1 mg QD for 10 days
- Safety assessments included physical examinations, vital signs, electrocardiograms, clinical laboratory assessments, and monitoring of adverse events
  - Subgroups planned for evaluation of safety and tolerability included age (< or ≥50 years), sex, race, and body mass index (BMI; < or ≥25 kg/m^2)
- Whole blood samples were collected for pharmacogenomic evaluation of baseline NTCP polymorphisms, with additional whole exome sequencing performed to characterize variants in BA transporters, cytochrome P450 enzymes, human leukocyte antigens, and uridine 5'-diphospho-glucuronosyltransferases with potential associations with safety observations
- Plasma total bile acid (tBA) concentrations were measured by enzymatic colorimetric assay, and changes were quantified as a pharmacodynamic biomarker

Results

- Overall, 40 HPs were enrolled in the study (SD cohorts, 16; MD cohorts, 24; **Figure 1**)
- All HPs in the SD cohorts completed treatment per protocol
- In the MD cohorts, 23/24 (96%) HPs completed treatment per protocol
  - One HP assigned to 1 mg ABI-6250 QD discontinued treatment on Day 8 due to a Grade 1 treatment-emergent adverse event (TEAE) of increased alanine aminotransferase (ALT)

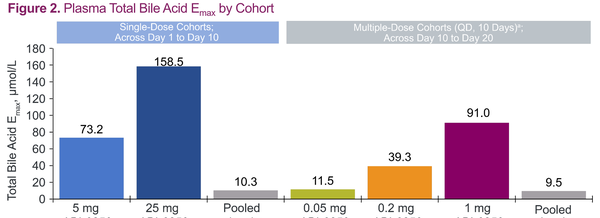
Table 1. Baseline Demographics

Characteristics	Single-Dose Cohorts: 5 mg ABI-6250 (n=6)	Single-Dose Cohorts: 25 mg ABI-6250 (n=6)	Single-Dose Cohorts: Pooled PBO (n=4)	Multiple-Dose Cohorts: 0.05 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 0.2 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 1 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: Pooled PBO (n=6)
Age, median (range), y	25.5 (21-33)	26.0 (20-29)	27.5 (21-40)	31.0 (21-57)	37.0 (25-49)	34.0 (21-50)	32.5 (29-52)
Sex[a]							
Male, n (%)	5 (83.3)	6 (100.0)	4 (100.0)	5 (83.3)	5 (83.3)	4 (66.7)	6 (100.0)
Female, n (%)	1 (16.7)	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0
Race[b]							
White, n (%)	2 (33.3)	5 (83.3)	3 (75.0)	5 (83.3)	4 (66.7)	6 (100.0)	6 (100.0)
Black/African American, n (%)	1 (16.7)	0	0	0	0	1 (16.7)	1 (16.7)
American Indian/Alaska Native, n (%)	1 (16.7)	0	0	1 (16.7)	0	1 (16.7)	0
Native Hawaiian/Pacific Islander, n (%)	0	1 (16.7)	0	0	0	0	0
Asian, n (%)	2 (33.3)	3 (50.0)	1 (25.0)	2 (33.3)	2 (33.3)	0	0
Other,[c] n (%)	1 (16.7)	0	0	0	0	1 (16.7)	0
BMI, median (range), kg/m^2	25.4 (19.4-26.6)	24.6 (23.6-29.9)	23.8 (22.3-26.3)	23.9 (20.0-24.8)	24.5 (20.7-30.3)	25.1 (22.5-29.8)	25.5 (22.7-30.5)

MD regimens were administered QD for 10 days. [a]Reported as sex assigned at birth. [b]5 mg ABI-6250 SD cohort: 1 HP reported White and American Indian/Alaska Native; 25 mg ABI-6250 SD cohort: 2 HPs reported White and Asian, 1 HP reported White and Native Hawaiian/Pacific Islander; 0.05 mg ABI-6250 MD cohort: 1 HP reported White and Asian, 1 HP reported White and American Indian/Alaska Native; 1 mg ABI-6250 MD cohort: 1 HP reported White and other, 1 HP reported White, Black/African American, and American Indian/Alaska Native; PBO MD cohort: 1 HP reported White and Black/African American. [c]Both HPs reported race as Maori.
BMI, body mass index; HP, healthy participant; MD, multiple-dose; PBO, placebo; QD, once daily; SD, single-dose; y, year.

- Overall, baseline demographics were generally similar between cohorts and consistent with a population of HPs (**Table 1**)
  - Overall, 35/40 (87.5%) HPs were male, 36/40 (90.0%) HPs were aged <50 years, 31/40 (77.5%) HPs were White, and 24/40 (60.0%) HPs had a BMI <25 kg/m^2

Figure 2. Plasma Total Bile Acid E_{max} by Cohort



[a]For multiple-dose cohorts, the baseline value is predose on Day 1.
E_{max}, maximum plasma total bile acid concentration determined directly from the concentration-time data; QD, once daily.

- Anticipated, asymptomatic, dose-dependent elevations in plasma tBA levels were observed (**Figure 2**)
  - Average maximum tBA levels for 0.2 mg ABI-6250 QD were similar to those reported for 2 mg BLV QD[13]

Table 2. Overall Safety Summary by Cohort

n (%) of Participants	Single-Dose Cohorts: 5 mg ABI-6250 (n=6)	Single-Dose Cohorts: 25 mg ABI-6250 (n=6)	Single-Dose Cohorts: Pooled PBO (n=4)	Multiple-Dose Cohorts: 0.05 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 0.2 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 1 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: Pooled PBO (n=6)
TEAEs	4 (66.7)	2 (33.3)	0	6 (100.0)	4 (66.7)	4 (66.7)	4 (66.7)
Grade 1	4 (66.7)	2 (33.3)	0	6 (100.0)	3 (50.0)	4 (66.7)	4 (66.7)
Grade 2	0	0	0	0	2 (33.3)[a]	0	0
≥Grade 3	0	0	0	0	0	0	0
TEAEs related to ABI-6250/PBO	0	0	0	1 (16.7)	0	2 (33.3)	0
TEAEs leading to ABI-6250/PBO DC	0	0	0	0	0	1 (16.7)[b]	0
TE SAEs	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0
TE graded laboratory abnormalities[c]	4 (66.7)	3 (50.0)	2 (50.0)	3 (50.0)	5 (83.3)	3 (50.0)	5 (83.3)
Grade 1	4 (66.7)	2 (33.3)	2 (50.0)	2 (33.3)	5 (83.3)	3 (50.0)	4 (66.7)
Grade 2	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	3 (50.0)
Grade 3	0	0	0	0	0	0	0
Grade 4	1 (16.7)[d]	0	0	0	0	0	0

Multiple-dose regimens were administered QD for 10 days. [a]Grade 2 TEAEs of headache and gout reported in different participants. [b]Grade 1 TEAE of increased ALT leading to treatment discontinuation. [c]Any postbaseline abnormality of Grade 1 or higher. [d]Grade 4 elevation in creatine kinase; Participant had Grade 2 elevation in creatine kinase at baseline.
ALT, alanine aminotransferase; DC, discontinuation; PBO, placebo; QD, once daily; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

- Overall, ABI-6250 was well tolerated, with no Grade ≥3 TEAEs, treatment-emergent serious adverse events, or deaths reported in any cohort (**Table 2**)
  - Grade 2 TEAEs of gout and headache were reported in 2 separate HPs receiving 0.2 mg ABI-6250 (**Table 2**)

Table 3. Summary of TEAEs by Cohort (>1 Participant Overall)

n (%) of Participants	Single-Dose Cohorts: 5 mg ABI-6250 (n=6)	Single-Dose Cohorts: 25 mg ABI-6250 (n=6)	Single-Dose Cohorts: Pooled PBO (n=4)	Multiple-Dose Cohorts: 0.05 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 0.2 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 1.0 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: Pooled PBO (n=6)
TEAEs (all grades)	4 (66.7)	2 (33.3)	0	6 (100.0)	4 (66.7)	4 (66.7)	4 (66.7)
URTI	1 (16.7)	0	0	1 (16.7)	0	0	1 (16.7)
Headache	2 (33.3)	0	0	0	1 (16.7)	2 (33.3)	0
Vessel puncture site bruise	0	0	0	3 (50.0)	1 (16.7)	0	1 (16.7)
Fatigue	0	0	0	2 (33.3)	0	0	0
Erythema	0	0	0	1 (16.7)	0	0	1 (16.7)
Back pain	0	0	0	0	0	0	2 (33.3)

Multiple-dose regimens were administered QD for 10 days.
PBO, placebo; QD, once daily; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

- Among HPs receiving ABI-6250, headache (2 HPs) was the most common TEAE in the SD cohorts, and vessel puncture site bruise (4 HPs) and headache (2 HPs) were the most common in the MD cohorts (**Table 3**)
  - No clinical adverse events associated with elevated tBA levels were reported (**Table 3**)

Table 4. Summary of Treatment-Emergent Graded Laboratory Abnormalities by Cohort (>1 Participant Overall)

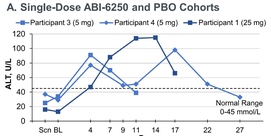
n (%) of Participants	Single-Dose Cohorts: 5 mg ABI-6250 (n=6)	Single-Dose Cohorts: 25 mg ABI-6250 (n=6)	Single-Dose Cohorts: Pooled PBO (n=4)	Multiple-Dose Cohorts: 0.05 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 0.2 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: 1 mg ABI-6250 (n=6)	Multiple-Dose Cohorts: Pooled PBO (n=6)
Postbaseline abnormalities (all grades)	4 (66.7)	3 (50.0)	2 (50.0)	3 (50.0)	5 (83.3)	3 (50.0)	5 (83.3)
Cholesterol (increased)							
Grade 1	1 (16.7)	2 (33.3)	1 (25.0)	0	0	1 (16.7)	0
Grade 2	0	0	0	1 (16.7)	1 (16.7)	0	0
ALT (increased)							
Grade 1	2 (33.3)	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)
Grade 2	0	1 (16.7)	0	0	0	0	0
Bicarbonate (decreased)							
Grade 1	0	0	1 (25.0)	0	1 (16.7)	0	0
Creatine kinase (increased)							
Grade 1	0	0	0	0	1 (16.7)	1 (16.7)	0
Grade 2	0	0	0	0	0	0	2 (33.3)
Grade 4	1 (16.7)[a]	0	0	0	0	0	0
Triglycerides (increased)							
Grade 1	1 (16.7)	0	0	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)
Sodium (decreased)							
Grade 1	0	0	0	1 (16.7)	1 (16.7)	0	1 (16.7)

Multiple-dose regimens were administered QD for 10 days. [a]Participant had Grade 2 elevation in creatine kinase at baseline.
ALT, alanine aminotransferase; PBO, placebo; QD, once daily.

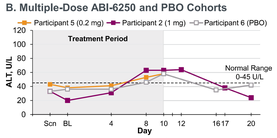
- Graded laboratory abnormalities occurring in >1 HP were (**Table 4**):
  - SD: increased cholesterol (3 ABI-6250, 1 PBO Grade 1); increased ALT (3 ABI-6250 [2 Grade 1, 1 Grade 2]); decreased bicarbonate (1 PBO [Grade 1]); increased creatine kinase (CK; 1 ABI-6250 [Grade 4]); increased triglycerides (1 ABI-6250 [Grade 1])
  - MD: increased cholesterol (3 ABI-6250 [1 Grade 1, 2 Grade 2]); increased ALT (2 ABI-6250, 1 PBO [Grade 1]); decreased bicarbonate (1 ABI-6250 [Grade 1]); increased CK (2 ABI-6250 [Grade 1], 2 PBO [Grade 2]); increased triglycerides (5 ABI-6250, 1 PBO [Grade 1]); decreased sodium (2 ABI-6250, 1 PBO [Grade 1])
- The only Grade >2 treatment-emergent graded laboratory abnormality was a single Grade 4 CK increase in an HP receiving 5 mg ABI-6250 (**Table 4**)
- Planned subgroup analyses according to age (< or ≥50 years of age), sex (male, female), race, and BMI (< or ≥25 kg/m^2) were too small for meaningful comparison

Figure 3. Treatment-Emergent ALT Elevations

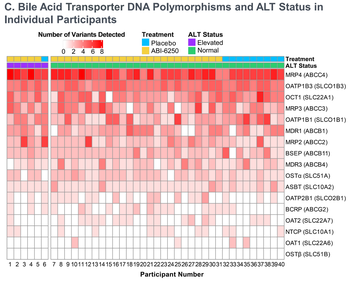
A. Single-Dose ABI-6250 and PBO Cohorts



B. Multiple-Dose ABI-6250 and PBO Cohorts



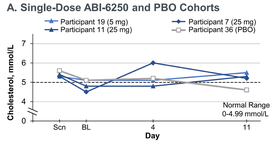
C. Bile Acid Transporter DNA Polymorphisms and ALT Status in Individual Participants



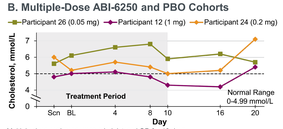
- Overall, ABI-6250 was well tolerated, with no Grade ≥3 TEAEs, treatment-emergent serious adverse events, or deaths reported in any cohort (**Table 2**)
  - Grade 2 TEAEs of gout and headache were reported in 2 separate HPs receiving 0.2 mg ABI-6250 (**Table 2**)
- Three HPs receiving SD ABI-6250 reported ALT elevations: two Grade 1 with 5 mg ABI-6250, one Grade 2 with 25 mg ABI-6250
- Two HPs receiving MD ABI-6250 (0.2 mg, 1 mg) and 1 receiving PBO reported ALT elevations, all Grade 1
- All elevations returned to within normal range, and there were no concurrent increases in bilirubin or international normalized ratio, decreases in albumin, or other findings consistent with declining hepatic function (**Figure 3**)

Figure 4. Treatment-Emergent Cholesterol Elevations

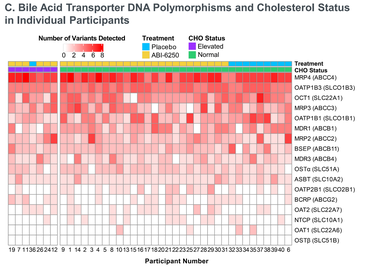
A. Single-Dose ABI-6250 and PBO Cohorts



B. Multiple-Dose ABI-6250 and PBO Cohorts



C. Bile Acid Transporter DNA Polymorphisms and Cholesterol Status in Individual Participants

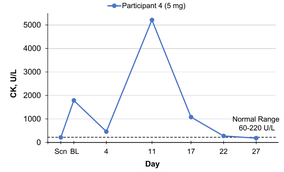


Multiple-dose regimens were administered QD for 10 days.
BL, baseline; CHO, cholesterol; PBO, placebo; QD, once daily; Scn, Screening.

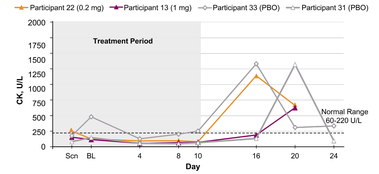
- All HPs with elevated cholesterol had levels above, or at, the upper limit of normal predose at Screening and/or Day 1
- No apparent dose dependency was observed
- In all HPs, cholesterol levels declined to baseline or within normal range with continued ABI-6250 dosing (**Figure 4**)

Figure 5. Treatment-Emergent Graded CK Elevations

A. Single-Dose ABI-6250 and PBO Cohorts



B. Multiple-Dose ABI-6250 and PBO Cohorts



Multiple-dose regimens were administered QD for 10 days.
BL, baseline; CK, creatine kinase; PBO, placebo; QD, once daily; Scn, Screening.

- One HP receiving a SD of 5 mg ABI-6250 had a Grade 2 CK increase (1790 U/L) predose on Day 1. CK declined to ungraded levels (463 U/L) at 3 days postdose. Following discharge, CK increased to a Grade 4 level (5210 U/L) at 10 days postdose and returned to ungraded levels at 20 days postdose (**Figure 5A**)
- Following MDs of ABI-6250 and PBO, CK levels were generally within the normal range during treatment. CK increases in ABI-6250 and PBO recipients occurred after completion of treatment in an outpatient setting (**Figure 5B**)
- The profiles of observed CK changes were generally consistent with those reported in Phase 1 studies in HPs[14,15]

Conclusions

- ABI-6250, a potent inhibitor of NTCP, was well tolerated with a favorable safety profile when administered orally, up to 25 mg as an SD, and up to 1 mg QD for 10 days in HPs
- Anticipated, asymptomatic, and dose-dependent elevations in tBA levels were observed
- Low-grade ALT and cholesterol increases were observed in both ABI-6250 and PBO recipients
- No associations between DNA polymorphisms in BA transporter genes were observed in HPs with elevations in ALT or cholesterol levels
- Planning for Phase 2 studies in patients with chronic HDV infection, PBC, and PSC is ongoing

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Disclosures

EJG is a member of scientific advisory boards for Aligos Therapeutics; Assembly Biosciences, Inc.; AusperBio; Gilead Sciences; GSK; Janssen; Precision BioSciences; Roche; Surrozen; Tune Therapeutics; Vir Biotechnology; and Vinon Therapeutics and has given sponsored lectures for AbbVie and Roche Diagnostics. **CS** is an employee and a stockholder of New Zealand Clinical Research. **GW**, **JL**, **NU**, **LL**, **SJK**, **AG**, and **KZ** are employees and stockholders of Assembly Biosciences, Inc.

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