Oral NTCP inhibitor ABI-6250 Elevates Bile Acids in a Randomized, Blinded, Phase 1a Study in Healthy Subjects

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Edward J. Gane[1], Christian Schwabe[2], Katie Zomorodi[3], Jinghu Carl Li[3], Sam Kim[3], Lewyn Li[3], Grace Wang[3], Anuj Gaggar[3], Mathias Haag[4], Matthias Schwab[4,5]

[1]University of Auckland, Auckland, New Zealand; [2]New Zealand Clinical Research, Auckland, New Zealand; [3]Assembly Biosciences, Inc., South San Francisco, CA, USA; [4]Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; [5]Departments of Clinical Pharmacology and of Biochemistry and Pharmacy, University of Tuebingen, Tuebingen, Germany

Background

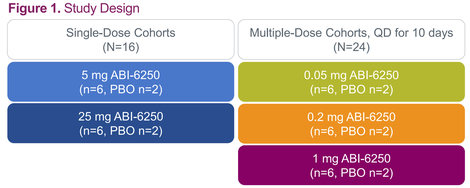
- The sodium taurocholate cotransporting polypeptide (NTCP) mediates the uptake of conjugated bile acid (BA) levels from the portal blood to the liver[1-3]
- NTCP inhibition leads to elevated circulating BAs and decreased intrahepatic BAs[4,5]
- In primary biliary cholangitis (PBC) and primary sclerosing 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 (PDs) of ABI-6250 in healthy participants (HPs; **Figure 1**)

Objective

- To assess the PDs of ABI-6250 following single-dose (SD) and multiple-dose (MD) administration in HPs as measured by changes in plasma total BAs (tBAs) and fractional BAs (fBAs)

Methods

Figure 1. Study Design



Key Inclusion Criteria
- Male or female
- Age ≥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 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**)
- The 2 SD cohorts and 3 MD cohorts enrolled 8 HPs each: 6 HPs received ABI-6250 and 2 received 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
- Changes in plasma BAs were quantified as a PD marker of NTCP inhibition. Plasma tBA concentrations were measured by enzymatic colorimetric assay, and plasma fBA concentrations (including glycine-conjugated BA [GCBA], taurine-conjugated BA [TCBA], and unconjugated BA [UCBA] concentrations) were measured by liquid chromatography-mass spectrometry (LC-MS)
  - GCBA: glycocholic acid, glycochenodeoxycholic acid, glycodeoxycholic acid, glycolithocholic acid, and glycoursodeoxycholic acid
  - TCBA: taurocholic acid, taurochenodeoxycholic acid, taurodeoxycholic acid, taurolithocholic acid, and tauroursodeoxycholic acid
  - UCBA: cholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and ursodeoxycholic acid
- Maximum plasma PD levels (E_{max}) were determined directly from the concentration-time data; area under the plasma PD concentration-time curve over 24 hours ($AUEC_{0\text{-}24}$) was calculated using non-compartmental methods

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 the 1-mg ABI-6250 QD cohort, discontinued treatment on Day 8 due to a Grade 1 treatment-emergent adverse event of increased alanine aminotransferase

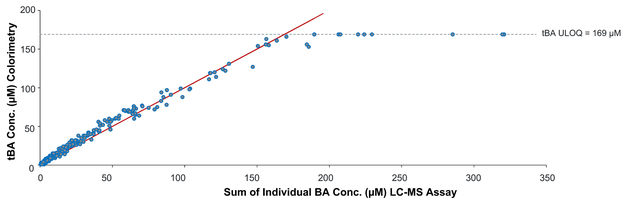
Table 1. Demographic Characteristics

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, male, n (%)	5 (83.3)	6 (100.0)	4 (100.0)	5 (83.3)	5 (83.3)	4 (66.7)	6 (100.0)
Race, White, n (%)	2 (33.3)	5 (83.3)	3 (75.0)	5 (83.3)	4 (66.7)	6 (100.0)	6 (100.0)
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)

Multiple-dose regimens were administered QD for 10 days.
BMI, body mass index; PBO, placebo; QD, once daily.

- Baseline demographics were generally similar between cohorts and consistent with a HP population (**Table 1**)
  - Across all cohorts, 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. Correlation Between tBA Levels and Sum of Individual fBA Levels



tBA levels above ULOQ of 169 µM were set to 169 µM.
conc, concentration; fBA, fractional bile acid; LC-MS, liquid chromatography-mass spectrometry; tBA, total bile acid; ULOQ, upper limit of quantitation

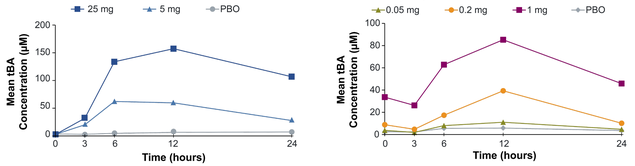
- The tBA levels from the colorimetric assay and fBA levels from the LC-MS were highly correlated, suggesting both methods are accurate and well calibrated (**Figure 2**)
- The upper limit of quantification (ULOQ) of the tBA method (colorimetry) was 169 µM as defined by the dilution factor used. The fBA method (LC-MS) covered a larger range of concentrations beyond 169 µM up to 321 µM

Table 2. Summary [Mean (CV%)] of Plasma BA Parameters Following Single and Multiple Doses of ABI-6250

Mean (CV%)	Single-Dose Cohorts[a]: 5 mg ABI-6250 (n=6)	Single-Dose Cohorts[a]: 25 mg ABI-6250 (n=6)	Single-Dose Cohorts[a]: Pooled PBO (n=4)	Multiple-Dose Cohorts[b]: 0.05 mg ABI-6250 (n=6)	Multiple-Dose Cohorts[b]: 0.2 mg ABI-6250 (n=6)	Multiple-Dose Cohorts[b]: 1 mg ABI-6250 (n=5)[c]	Multiple-Dose Cohorts[b]: Pooled PBO (n=6)
tBA parameters							
Baseline, µM	2.83 (52)	2.50 (42)	3.50 (72)	3.83 (51)	3.67 (54)	4.70 (147)	3.58 (108)
E_{max}, µM	73.17 (42)	158.5 (14)	10.25 (26)	11.50 (38)	39.33 (31)	91.00 (26)	9.50 (39)
$AUEC_{0\text{-}24}$, h*µM	1048.0 (35)	2758.0 (16)	137.6 (11)	174.4 (31)	520.3 (26)	1453.0 (27)	109.6 (29)
GCBA parameters							
Baseline, µM	1.17 (92)	0.80 (43)	1.34 (124)	1.88 (58)	1.13 (52)	0.94 (60)	1.57 (118)
E_{max}, µM	63.20 (49)	187.4 (31)	5.99 (22)	9.11 (43)	25.43 (27)	78.79 (29)	5.24 (30)
$AUEC_{0\text{-}24}$, h*µM	856.0 (45)	2565.1 (16)	69.77 (11)	132.1 (34)	317.5 (24)	1172.7 (28)	63.46 (42)
TCBA parameters							
Baseline, µM	0.08 (66)	0.09 (44)	0.19 (126)	0.21 (141)	0.17 (93)	0.08 (53)	0.12 (76)
E_{max}, µM	5.69 (55)	37.30 (50)	0.49 (51)	0.82 (22)	3.36 (58)	11.59 (40)	0.52 (44)
$AUEC_{0\text{-}24}$, h*µM	74.28 (49)	520.1 (51)	6.45 (43)	11.95 (25)	41.86 (58)	167.2 (38)	6.74 (47)
UCBA parameters							
Baseline, µM	0.84 (84)	0.66 (81)	1.08 (56)	1.31 (83)	1.21 (51)	2.62 (194)	1.20 (88)
E_{max}, µM	6.93 (89)	15.13 (95)	2.51 (29)	1.72 (36)	3.28 (55)	5.34 (56)	2.59 (117)
$AUEC_{0\text{-}24}$, h*µM	60.02 (66)	60.66 (63)	25.69 (30)	24.24 (39)	25.55 (55)	53.33 (56)	12.83 (33)

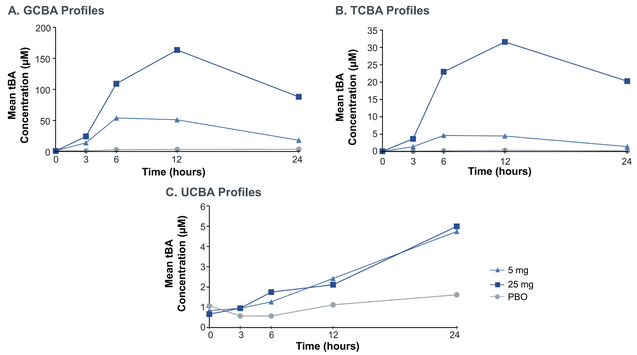
Multiple-dose regimens were administered QD for 10 days.
[a]For single-dose cohorts, the baseline level is pre-dose on Day 1, E_{max} is across Day 1 to Day 10, $AUEC_{0\text{-}24}$ is across Day 1. [b]For multiple-dose cohorts, the baseline level is pre-dose on Day 1, E_{max} is across Day 10 to Day 20, $AUEC_{0\text{-}24}$ is across Day 10. [c]Day 10 data for one participant are excluded due to early discontinuation on Day 8.
$AUEC_{0\text{-}24}$, area under the PD concentration-time curve from time zero to 24 hours; BA, bile acid; CV, coefficient of variation; E_{max}, maximum plasma PD level determined directly from the concentration-time data; GCBA, glycine-conjugated bile acid; PBO, placebo; QD, once daily; PD, pharmacodynamic; tBA, total bile acid; TCBA, taurine-conjugated bile acid; UCBA, unconjugated bile acid.

Figure 3. Mean Plasma tBA Profiles Following SD Administration on Day 1 and MD Administration on Day 10



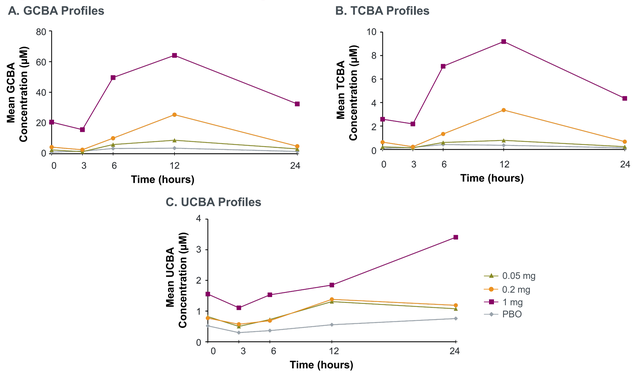
Multiple-dose regimens were administered QD for 10 days.
MD, multiple dose; PBO, placebo; QD, once daily; SD, single dose; tBA, total bile acid.

Figure 4. Mean Plasma fBA Profiles Following SD Administration on Day 1, First 24 Hours



fBA, fractional bile acid; GCBA, glycine-conjugated bile acid; PBO, placebo; SD, single dose; TCBA, taurine-conjugated bile acid; UCBA, unconjugated bile acid.

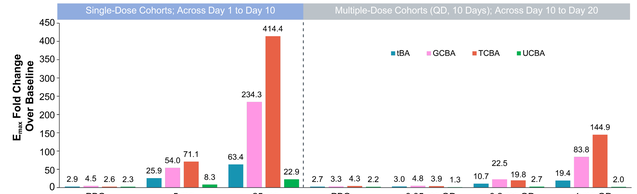
Figure 5. Mean Plasma fBA Profiles Following MD Administration on Day 10, First 24 Hours



fBA, fractional bile acid; GCBA, glycine-conjugated bile acid; MD, multiple dose; PBO, placebo; TCBA, taurine-conjugated bile acid; UCBA, unconjugated bile acid.

- Following a single administration and multiple QD administrations of ABI-6250, tBA, GCBA, and TCBA levels increased in a dose-dependent manner (**Table 2** and **Figures 3-5**)
- GCBA concentrations were generally higher than TCBA and UCBA concentrations in all cohorts (**Figures 4 and 5**)

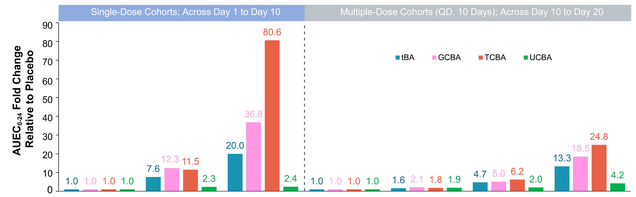
Figure 6. Conjugated and Unconjugated fBA and tBA E_{max} Fold Change over Baseline By Cohort (Based on Mean Values)



E_{max} is determined directly from concentration-time data.
E_{max}, maximum plasma PD level; fBA, fractional bile acid; GCBA, glycine-conjugated bile acid; PBO, placebo; PD, pharmacodynamic; QD, once daily; tBA, total bile acid; TCBA, taurine-conjugated bile acid; UCBA, unconjugated bile acid.

- Compared with baseline on Day 1, dose dependent increases of ≥26-fold in tBA, GCBA, and TCBA E_{max} levels were observed following SD administration of 5 mg and 25 mg on Day 1 (**Figure 6**)
- Compared with baseline on Day 1, dose dependent increases of ≥11-fold in tBA, GCBA, and TCBA E_{max} levels were observed following MD administration of 0.2 mg and 1 mg on Day 10 (**Figure 6**)

Figure 7. Conjugated and Unconjugated fBA and tBA $AUEC_{0\text{-}24}$ Fold Change Relative to PBO By Cohort (Based on Mean Values)



AUEC0-24, area under the PD concentration-time curve from time zero to 24 hours; fBA, fractional bile acid; GCBA, glycine-conjugated bile acid; PD, pharmacokinetic; PBO, placebo; QD, once daily; tBA, total bile acid; TCBA, taurine-conjugated bile acid; UCBA, unconjugated bile acid.

- Compared with PBO, dose dependent increases of ≥8-fold in tBA, GCBA, and TCBA $AUEC_{0\text{-}24}$ were observed following SD administration of 5 mg and 25 mg on Day 1 (**Figure 7**)
- Compared with PBO, dose dependent increases of ≥5-fold in tBA, GCBA, and TCBA $AUEC_{0\text{-}24}$ were observed following MD administration of 0.2 mg and 1 mg on Day 10 (**Figure 7**)

Conclusions

- ABI-6250, a potent inhibitor of NTCP, was well tolerated with a favorable safety profile[13] when administered orally at up to 25 mg as a SD and up to 1 mg QD for 10 days in HPs
- Pharmacodynamic data showed target engagement at a dose as low as 0.2 mg QD
- tBA levels and sum of individual fBA levels were in close agreement and below the tBA ULOQ suggesting both methods are accurate and well calibrated
- GCBA levels were generally higher than TCBA and UCBA levels in all cohorts
- The elevations in tBA and fBA levels observed with ABI-6250 are consistent with those reported for BLV, a specific inhibitor of NTCP, and indicate potent target engagement by ABI-6250[11,14]
- Further fBA analysis showed that GCBA and TCBA levels, measures of on-target NTCP engagement, increased in a dose-dependent manner
- In contrast, UCBA levels, which are not selective NTCP substrates, were not meaningfully impacted

References

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Disclosures

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