Preliminary safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of AB-101, a small molecule PD-L1 inhibitor, in healthy and chronic hepatitis B (CHB) subjects

Edward Gane[1], Marta Dobrayanska[2], Alina Jucov[3], Man-Fung Yuen[4], Grace Lai Hung Wong[5], Emily P. Thi[6], Timothy Eley[6], Sharie C. Ganchua[6], Christine Espiritu[6], Varun Sharma[6], Reddy Pamulapati[6], Andrew G. Cole[6], Gavin D. Heffernan[6], Seyma Ozturk[6], Angela M. Lam[6], Troy O. Harasym[6], Ravi R. Dugyala[6], Michael J. Sofia[6], Karen D. Sims[6], Tilly Varughese[6]

[1]University of Auckland, Auckland, New Zealand; [2]Arensia Exploratory Medicine, Ukraine; [3]Arensia Exploratory Medicine GmbH, Düsseldorf, Germany, and Nicolae Testemițanu State University of Medicine and Pharmacy, Chişinău, Moldova; [4]The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [5]Medical Data Analytics Centre, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China; [6]Arbutus Biopharma, Warminster, Pennsylvania, USA

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BACKGROUND

- Functional cure of CHB requires suppression of viral replication, reduction of HBV antigens (particularly HBsAg) and induction of anti-HBV immune responses. The PD-1/PD-L1 immune checkpoint axis plays a key role in HBV immune tolerance, which is a critical driver of chronic hepatitis B (CHB) persistence.
- PD-1/PD-L1 checkpoint inhibition via immune checkpoint inhibitor antibodies (ICI Abs) has been associated with HBsAg loss and seroconversion in CHB subjects with low baseline HBsAg.
- A concern with the use of ICI Abs in CHB patients is the development of immune related adverse events (irAEs).
- AB-101 is an oral small molecule PD-L1 inhibitor with favorable liver distribution in preclinical species and the potential to enable tunable on-target engagement while reducing toxicities with systemic exposure.[1]
- AB-101-001 is an ongoing 3-part Phase 1a/1b study evaluating safety, pharmacokinetics (PK) and pharmacodynamics (PD) of AB-101 in healthy subjects (HS) (Parts 1 and 2) and CHB subjects (Part 3). Here we report data from Parts 1, 2 and preliminary data from the first CHB cohort of Part 3 (3A).

OBJECTIVES

- Evaluate the safety and tolerability of AB-101 following oral administration of single and multiple doses to healthy and CHB subjects
- Characterize single dose and steady-state PK of AB-101 in healthy and CHB subjects
- Assess PD via receptor occupancy (RO) of AB-101 in healthy and CHB subjects

MATERIALS AND METHODS

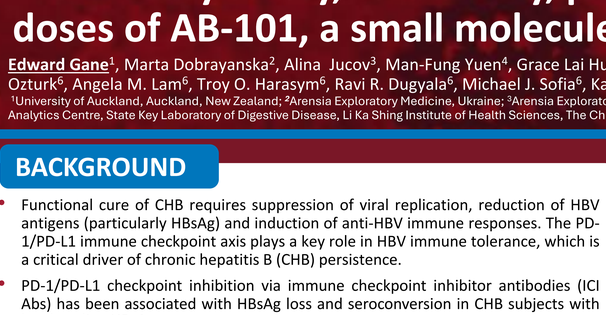


Figure 1: AB-101-001 Clinical Study Design

- Key eligibility criteria used for HS include:
  - Males aged 18 to 50 years of age; Body mass index (BMI) ≥ 18 kg/m² and ≤ 35 kg/m²
  - No history of clinically significant GI, hematologic, renal, hepatic, bronchopulmonary, neurological, autoimmune, psychiatric or CV disease
  - No clinically significant abnormalities of laboratory test results, ECGs, or vital sign measurements
- Key eligibility criteria used for CHB subjects include:
  - Males and females aged 18 to 50 years of age; BMI ≥ 18 kg/m2 and ≤ 35 kg/m²
  - Documented chronic HBV infection (HBsAg positive or HBV DNA positive >6 months prior to Screening and negative HBsAb IgM)
  - HBsAg ≥ 100 IU/mL, HBV DNA < LLOQ and taking nucleos(t)ide analog therapy (NA; TAF, TDF, or entecavir) for at least 6 months
  - No evidence of cirrhosis, advanced fibrosis, or HCC via Fibroscan (≤8.5 kPa) and liver ultrasound
  - No history or evidence of autoimmune disease, untreated chronic infections, or latent infections
- Safety and tolerability were monitored throughout the study via collection of treatment emergent adverse events (TEAEs), immune related adverse events (irAEs), physical examinations, vital signs, ECGs and clinical laboratory testing
  - Duration of follow up was extensive to ensure collection of data to evaluate presence of immediate and delayed irAEs (Part 1– 56 days; Part 2 – 84 days; Part 3 – 168 days post-dosing)
- PD was assessed via measurement of PD-L1 levels associated with peripheral cells using a proprietary method
- PK parameters were derived via non-compartmental analysis using Phoenix Win-nonlin (Certara, Princeton, NJ, USA) version 8 or higher

RESULTS

Table 1: SAD Healthy Subject (HS) Baseline Characteristics

Baseline Measure	Cohort 1A 1 mg N = 6	Cohort 1B 3 mg N = 6	Cohort 1C 10 mg N = 6	Cohort 1D 25 mg N = 6	Cohort 1E 40 mg N = 6	Pooled Placebo N = 10
Age (years) [Mean (SD)]	23.7 (4.5)	29.5 (4.0)	27.5 (5.8)	25.3 (4.7)	29.7 (6.4)	27.7 (7.9)
BMI (kg/m²) [Mean (SD)]	24.9 (2.2)	26.2 (3.9)	22.7 (2.2)	24.0 (3.9)	25.2 (3.1)	25.3 (3.7)
Male Gender [n (%)]	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	10 (100)
Race [n (%)]						
Asian	3 (50)	2 (33.3)	0	1 (16.7)	1 (16.7)	3 (30)
White	3 (50)	3 (50)	3 (50)	4 (66.7)	4 (66.7)	6 (60)
Black/African American	0	0	0	0	0	0
Pacific Islander/Native Hawaiian	0	0	0	0	0	0
Other	0	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (10)
Not reported	0	1 (16.7)	2 (33.3)	0	0	0

Table 2: MAD Healthy Subject (HS) Baseline Characteristics

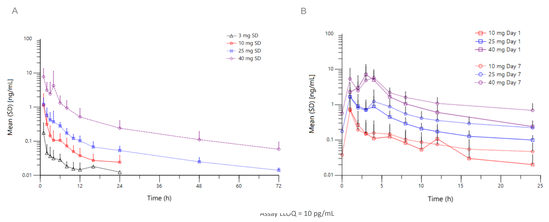
Baseline Measure	Cohort 2A 10 mg QD x 7 days N = 8	Cohort 2B 25 mg QD x 7 days N = 8	Cohort 2C 40 mg QD x 7 days N = 8	Pooled Placebo N = 6
Age (years) [Mean (SD)]	36.0 (8.1)	32.1 (9.1)	30.3 (7.7)	28.2 (4.8)
BMI (kg/m²) [Mean (SD)]	28.4 (3.8)	26.1 (3.0)	25.2 (3.6)	25.1 (1.8)
Male Gender [n (%)]	8 (100)	8 (100)	8 (100)	6 (100)
Race [n (%)]				
Asian	2 (25)	2 (25)	2 (25)	0
White	3 (37.5)	5 (62.5)	1 (12.5)	4 (66.7)
Black/African American	0	0	0	1 (16.7)
Pacific Islander/Native Hawaiian	0	0	0	0
Other	1 (12.5)	1 (12.5)	4 (50)	1 (16.7)
Multiple	2 (25)	0	1 (12.5)	0

Table 3: CHB Subject Baseline Characteristics

Baseline Measure	Cohort 3A 10mg QD x 28 days N = 10	Cohort 3A Placebo QD x 28 days N=2
Age (years) [Mean (SD)]	43.1 (11.2)	41.5 (10.6)
BMI (kg/m²) [Mean (SD)]	24.27 (3.6)	24.55 (6.3)
Male Gender [n (%)]	9 (90)	2(100)
Race [n (%)]		
Asian	2 (20)	1 (50)
White	7 (70)	1 (50)
Pacific Islander/Native Hawaiian	1 (10)	0
HBeAg+ [n (%)]	2 (20)	1 (50)
ALT (U/L) [Mean (SD)]	33.2 (30)	23.5 (7.8)
HBsAg (Log_{10} IU/mL) [Mean (SE)]	3.3 (0.50)	3.1 (0.5)

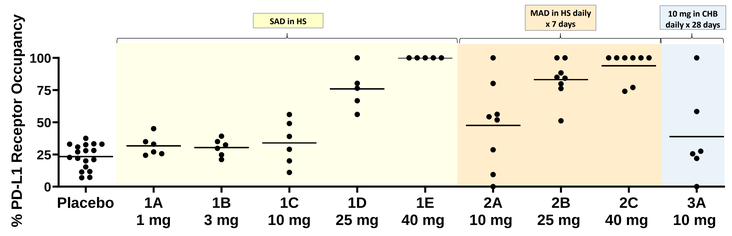
HBV genotypes pending

Figure 2: AB-101 Plasma Concentration vs. Time SAD (A) and MAD (B)



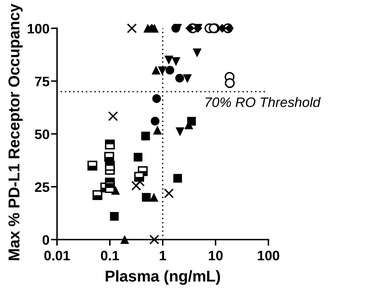
- Plasma concentrations of AB-101 were very low, consistent with extensive distribution to liver, as observed in preclinical species
- AB-101 appeared rapidly in plasma with maximum concentrations generally 1-3 hours post dose
- T-HALF was shorter and more variable at low doses likely due to assay limitations
- After 7 days of QD administration, modest accumulation was observed
- The PK at the 40 mg dose was clearly more than dose proportional possibly due to saturation of intestinal P-gp (efflux ratio of ~28 in Caco-2 cells, data not shown)
- PK sampling in CHB subjects was limited to 6 hours post dose on Day 1 and Day 28. Concentrations over this interval were comparable to HS (data not shown)

Figure 3: Dose Responsive Increases in PD-L1 Receptor Occupancy



- Receptor occupancy increases in healthy subjects with increasing dose
- Saturation of receptor occupancy observed at 40 mg AB-101 dose of AB-101
- No apparent accumulation of receptor occupancy with AB-101 repeat dosing
- No changes noted in HBsAg, HBV RNA or HBcrAg quantitative levels in CHB subjects in Cohort 3A; this was not unexpected as subjects received only 28 days of AB-101 dosing and subjects were required to have HBsAg ≥100 IU/mL at screening
  - Prior studies suggest that HBsAg reductions are observed following PD-1/PD-L1 inhibitor treatment in subjects with HBsAg <100 IU/mL[3]

Figure 4: PD-L1 Receptor Occupancy Increases as AB-101 Plasma Concentration Increases



PD-L1 receptor occupancy (RO) is associated with AB-101 plasma concentrations in healthy subjects and chronic hepatitis B subjects following single or multiple doses of AB-101. Shown are maximum % PD-L1 receptor occupancy for each individual subject through to 7 days post-last dose administration with that subject's maximum AB-101 plasma concentration. 70% RO threshold considered maximum receptor occupancy.

- Dose responsive increase in RO observed with increasing AB-101 plasma concentrations
- Saturation in RO mostly observed at AB-101 plasma concentrations >1 ng/mL
- Trends are similar to PK-PD association observed in preclinical mouse efficacy models (see Poster THU-254)[2]

Table 4: Summary Statistics of AB-101 PK Parameters

PK Parameter - SAD	Cohort 1A 1 mg [N = 6]	Cohort 1B 3 mg [N = 6]	Cohort 1C 10 mg [N = 6]	Cohort 1D 25 mg [N = 6]	Cohort 1E 40 mg [N = 6]
Cmax (ng/mL) [Geo Mean (SD)]	NR	0.122 (94)	0.635 (116)	1.22 (42)	5.55 (79)
Tmax (h) [Median (min-max)]	NR	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-4.0)	1.0 (1.0-4.0)
AUCinf (ng*h/mL) [Geo Mean (SD)]	NR	0.473 (70)	1.82 (92)	6.24 (27)	26.6 (76)
T-HALF (h) [Mean (SD)]	NR	7.8 (3.9)	7.1 (3.2)	24.2 (4.0)	21.6 (4.6)

PK Parameter - MAD	Cohort 2A 10 mg QD [N = 8]		Cohort 2B 25 mg QD [N = 8]		Cohort 2C 40 mg QD [N = 8]	
Study Day	1	7	1	7	1	7
Cmax (ng/mL) [Geo Mean (SD)]	0.484 (108)	0.336 (149)	1.42 (77)	1.68 (63)	6.86 (62)	7.51 (66)
Tmax (h) [Median (min-max)]	1.0 (1.0-12.0)	1.0 (1.0-2.0)	1.0 (1.0-4.0)	1.0 (1.0-6.0)	3.0 (1.0-4.0)	3.0 (1.0-6.0)
AUCtau (ng*h/mL) [Geo Mean (SD)]	1.67 (109)	2.01 (102)	6.79 (54)	10.6 (54)	25.8 (56)	36.8 (56)

Cmax = maximum plasma concentration; Tmax = time of maximum concentration; AUCinf = Area under the concentration vs. time curve extrapolated to infinite time, reported for SAD cohorts; AUCtau = Area under the concentration vs. time curve over the dosing interval, reported for MAD cohorts, after 7 days of dosing; T-HALF = elimination half-life; QD = once daily; Geo Mean = geometric mean; CV = coefficient of variation; SD = standard deviation; NR = not reported/insufficient data

Table 5: Adverse Events in Healthy Subjects (HS) and CHB Subjects

Subjects, n (%)	Part 1, SAD HS						Part 2, MAD QD x 7 days, HS				Part 3, CHB QD x 28 days	
	1 mg N=6	3 mg N=6	10 mg N=6	25 mg N=6	40 mg N=6	PBO N=10	10 mg N=8	25 mg N=8	40 mg N=8	PBO N=6	10 mg N=10	PBO N=2
Subjects with any TEAE [N (%)]	3 (50)	3 (50)	5 (83.3)	4 (66.6)	2 (33.3)	7 (70.0)	7 (87.5)	7 (87.5)	6 (75)	5 (83.3)	4∞ (40.0)	0
TEAE Severity												
Grade 1	3	3	5	2	2	6	5	6	3	4	2	0
Grade 2	0	0	0	2	0	1	2	1	3	1	1	0
Grade 3	0	0	0	0	0	0	0	0	0	0	1	0
Related TEAEs [N (%)]	1* (16.6)	0	0	0	0	0	1† (12.5)	0	1‡ (12.5)	2 (33.3)	2§ (20)	0
ALT elevation	0	0	0	0	0	0	0	0	0	0	2	0
Grade 1											2	
Grade 2											0	

SAD = single ascending dose; MAD = multiple ascending doses; QD = once daily; CHB = chronic hepatitis B; PBO = placebo; TEAE = Treatment emergent adverse event; *Grade 1 fatigue, related; †Grade 1 headache, related; ‡Grade 1 abdominal pain and diarrhea, related; ∞ 6 TEAEs in 4 subjects in Cohort 3A. 4/6 TEAEs were unrelated in 3 subjects. Unrelated TEAEs were Grade 3 obesity and Grade 1 ALT elevation in 1 subject due to high fat diet and sedentary lifestyle; Grade 1 fatigue and Grade 1 diarrhea in the other 2 subjects § Related TEAEs of Grade 1 ALT elevation and Grade 2 reactive gastropathy in 1 subject. ALT elevation improved while receiving AB-101 during the treatment period. Subject had history of GERD not on therapy at baseline.

- AB-101 was well tolerated in both HS and CHB subjects
- The most common TEAEs in HS were fatigue, headache, and dermatitis secondary to medical devices (i.e. ECG stickers, Holter monitors)
- Except the unrelated Grade 3 obesity TEAE in Cohort 3A, there were no other Grade 3 or 4 TEAEs reported in any of the other cohorts
- There were no deaths, SAEs, irAEs, or early discontinuations due to AB-101 in any cohort
- Two subjects withdrew from the study, one each in Cohort 1E and 2C
- There were three isolated Grade 4 creatine kinase elevations in HS due to strenuous exercise, but all instances were in placebo subjects. None were reported as AEs. There were no other clinically significant changes in laboratory values, vital signs, physical examinations or ECGs

CONCLUSIONS

- Single doses of AB-101 up to 40 mg and repeat doses up to 40 mg once daily for 7 days were well tolerated in healthy subjects
- Dosing AB-101 at 10 mg once daily for 28 days in CHB subjects was also well tolerated with few TEAEs reported
- There were no SAEs or immune related adverse events reported in healthy subjects or in the first CHB subject cohort
- Preliminary PD data showed PD-L1 receptor occupancy at doses ≥10 mg with dose-responsive increases observed, saturating at single and multiple once daily doses of 40 mg of AB-101 in healthy subjects
- Assessment of the safety, tolerability and the relationship between RO, antiviral activity and AB-101 exposures in CHB subjects in Cohort 3B are ongoing

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3. J Qian, et al. Hepatology. 81(4):1328-1342, 2025

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CONTACT INFORMATION AND DISCLOSURES

Corresponding author: Tilly Varughese, MD Email: tvarughese@arbutusbio.com
Medical Director, Clinical Development
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA 18974

Edward Gane has a relationship with AbbVie, Roche, GSK, Aligos, AusperBio, Gilead Sciences, GSK, Precision Bio, Tune Therapeutics, Virion and Vir Bio. Authors affiliated with Arbutus Biopharma are employees and may own company stock.