Long-term HBsAg suppression maintained after cessation of AB-729 treatment and comparable on-treatment response observed in HBeAg+ subjects

Man-Fung Yuen[1], Elina Berliba[2], Wattana Sukeepaisarnjaroen[3], Jacinta Holmes[4], Apinya Leerapun[5], Pisit Tangkijvanich[6], Simone I Strasser[7], Alina Jucov[2], Edward Gane[8], Emily P Thi[9], Heather Sevinsky[10], Elina Medvedeva[10], Varun Sharma[10], Kevin Gray[10], Deana Antoniello[10], Gaston Picchio[10], Karen D Sims[10], Timothy Eley[10].

[1]Queen Mary Hospital, The University of Hong Kong, Hong Kong, [2]Arensia Exploratory Medicine, Moldova, [3]Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand, [4]St. Vincent's Hospital, Melbourne, Australia, [5]Chiang Mai University Chiang Mai, Thailand, [6]Chulalongkorn University, Bangkok, Thailand, [7]Royal Prince Alfred Hospital, Sydney, Australia, [8]Auckland Clinical Studies, New Zealand, [9]Arbutus Biopharma Discovery and Research, [10]Arbutus Biopharma Clinical Development

22-26 JUNE 2022 LONDON · EASL The Home of Hepatology · SAT443

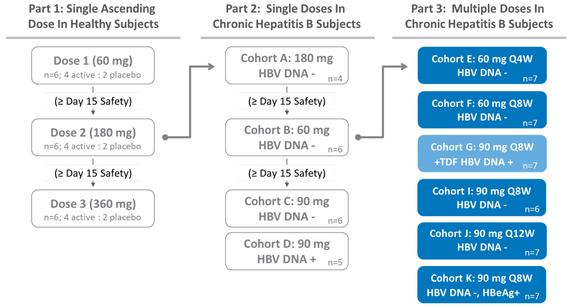
Arbutus BIOPHARMA *Curing Chronic Hepatitis B*

BACKGROUND

- Current therapies for chronic hepatitis B (CHB) slow or prevent the development of HBV-related liver complications, but do not typically lead to a cure.[1,2,3] Thus, there is an unmet medical need for new finite HBV therapies that have the potential to provide a functional cure for CHB.
- AB-729 is a subcutaneously administered *N*-Acetylgalactosamine(GalNAc)-conjugated single trigger pan-genotypic RNA interference therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens. AB-729 targets the liver via proprietary technology based on GalNAc-ligand interaction with the asialoglycoprotein receptor (ASGPR). AB-729 is in Phase 2 clinical development for the treatment of CHB in combination with other agents.
- AB-729-001 is a 3-part study examining the safety and pharmacodynamics (PD) of single and repeat doses of AB-729 in healthy subjects and CHB subjects (both untreated and virologically-suppressed on nucleos(t)ide analogue [NA] therapy), and preliminary data have been reported previously.[4,5,6,7]
- Here we report additional on-treatment and follow up data in CHB subjects following the last dose of AB-729, including the first reported data from a dedicated HBeAg+ cohort.
- Subjects meeting protocol-defined response criteria assessed at least 24 weeks after the last dose of AB-729 were given the option to discontinue NA therapy. More details for these subjects are presented in poster SAT448.

MATERIALS AND METHODS

Figure 1: AB-729-001 Study Design



- Cohorts E, F, I, J and K enrolled HBeAg positive and negative, HBV DNA- subjects on stable NA therapy. Cohort K enrolled HBeAg positive subjects only.
- Cohort G enrolled HBeAg positive and negative, HBV DNA+ subjects who began treatment with TDF concurrently with AB-729.
- All Part 3 repeat dose cohorts were initially designed for 24 weeks of treatment.
- Eligible subjects (>0.5 $\log_{10}$ HBsAg reduction at Week 20) had the option to continue AB-729 through Week 48; all 41 subjects were eligible; 40 subjects agreed.
- Cohort E switched from AB-729 60mg Q4W to 60mg Q12W for the extension phase while the remaining cohorts maintained their initial regimen.
- Subjects are followed for at least 48 weeks after completion of AB-729 treatment.
- Assay Methods:
  - HBV DNA quantified by Abbott Realtime HBV viral load assay, LLOQ = 10 IU/mL; <LLOQ = 5 IU/mL
  - HBsAg quantified by Roche Elecsys HBsAg II quant II, LLOQ = 0.07 IU/mL; <LLOQ = 0.035 IU/mL
  - HBcrAg quantified by Fujirebio Lumipulse G HBcrAg, LLOQ = 3.0 $\log_{10}$ U/mL; <LLOQ = 2.9 $\log_{10}$ U/mL
  - HBeAg quantified by Abbott Architect HBeAg, LLOQ = 0.11 IU/mL; <LLOQ = 0.055 IU/mL
  - ALT ULN = 48 U/L male, 43 U/L female

RESULTS

Table 1: Baseline Characteristics

Baseline Measure#	HBV DNA- Cohort E‡ (N=7)	Cohort F (N=7)	Cohort I (N=6)^	Cohort J (N=7)	Cohort K* (N=7)	HBV DNA+ Cohort G (N=7)
Age in years, mean (range)	45.1 (33 – 63)	44.0 (31 – 59)	45.7 (38 – 54)	44.3 (35 – 61)	41.4 (21 – 57)	43.9 (34 – 50)
Male gender, n (%)	4 (57)	4 (57)	4 (67)	5 (71)	4 (57)	3 (43)
BMI, mean (SD)	27.7 (5.0)	23.7 (2.2)	25.5 (3.1)	28.7 (4.8)	25.0 (4.7)	23.8 (4.0)
Race, n (%)						
Asian	1 (14)	5 (71)	5 (83)	4 (57)	6 (86)	6 (86)
Black	0	1 (14)	0	0	0	0
White	6 (86)	1 (14)	1 (17)	3 (43)	0	1 (14)
Pacific Islander	0	0	0	0	1 (14)	0
ALT (U/L), mean (SD)	22.4 (10.5)	23.4 (15.2)	26.0 (10.2)	20.1 (7.2)	25.1 (8.9)	32.7 (15.8)
HBV eAg negative, n (%)	7 (100)	6 (71)◊	5 (83)	4 (57)	0	7 (100)
HBsAg (IU/mL), mean (range)	5,372 (584 – 11,761)	5,354 (667 – 18,605)	4,691 (338 – 19,017)	6,911 (309 – 25,345)	2,221 (545 – 5,273)	1,818 (277 – 4,723)

#Genotype not determined; ‡Subjects switched to AB-729 60 mg Q12W for the extension phase; ^ N = 6 due to one subject meeting exclusion criteria on Day 1 and a replacement subject receiving an incorrect dose on Day 1; both entered follow up and were excluded from the analysis; ◊ One subject counted as HBeAg negative was identified as "HBeAg borderline" (baseline HBeAg = 0.18 IU/mL, LLOQ = 0.11 IU/mL); *Cohort K Mean (SD) Baseline HBeAg = 22.7 (37.5) IU/mL

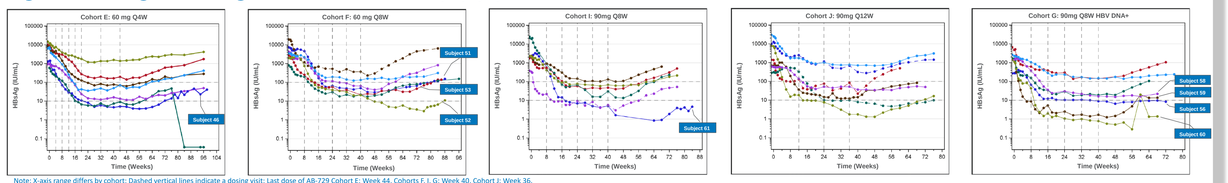
Table 2: Mean (SE) Baseline and Δ $\log_{10}$ HBsAg by Visit

Nominal Visit	HBV DNA- Cohort E (N=7)	Cohort F (N=7)	Cohort I (N=6)	Cohort J◊ (N=7)	Cohort K (N=7)	HBV DNA+ Cohort G (N=7)
Baseline (IU/mL)	3.51 (0.20)	3.53 (0.17)	3.36 (0.23)	3.37 (0.28)	3.23 (0.14)	3.14 (0.14)
Week 12	-1.10 (0.15)	-1.02 (0.11)	-1.30 (0.19)	-1.06 (0.31)	-1.63 (0.39)	-1.56 (0.32)
Week 24	-1.84 (0.16)	-1.57 (0.09)	-1.80 (0.23)	-1.56 (0.25)	-1.99 (0.35)	-1.82 (0.29)
Week 36	-1.84 (0.19)	-1.78 (0.10)	-2.06 (0.28)	-1.70 (0.39)	-2.50 (0.39)	-2.08 (0.32)
Week 48	-1.89 (0.18)	-1.90 (0.14)	1.91 (0.32)	-1.80* (0.41)		-2.15 (0.34)
Week 12 Post Last Dose	-1.81 (0.17)	-1.74 (0.16)	-1.77 (0.31)	-1.80* (0.41)		-1.97 (0.28)
Week 24 Post Last Dose	-1.54 (0.19)	-1.48 (0.24)	-1.67 (0.40)	-1.52 (0.40)		-1.59 (0.31)

Note: Last dose Cohort E, Week 44; Cohorts F, I, G, K: Week 40; Cohort J: Week 36; Mean (SE) values presented only if N≥5; ◊ one subject in Cohort J chose not to extend treatment after Week 24; *Week 48 and 12 weeks post last dose are at the same visit for Cohort J

- Mean declines in HBsAg on treatment and post treatment continue to be comparable across cohorts
- Results to date from a dedicated HBeAg+ cohort (Cohort K) further support preliminary observations suggesting that baseline HBeAg status has no effect on response

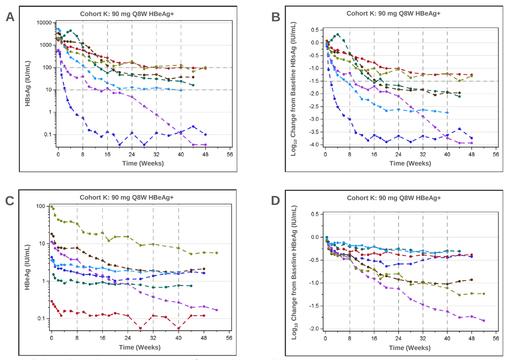
Figure 2: Change in HBsAg vs time for Cohorts E, F, I, J, and G



Note: X-axis range differs by cohort; Dashed vertical lines indicate a dosing visit; Last dose of AB-729 Cohort E: Week 44, Cohorts F, I, G: Week 40, Cohort J: Week 36.

- Robust declines in HBsAg were observed in most subjects and maintained well after the cessation of AB-729 treatment; mean log change from baseline 24 weeks post last dose is approximately -1.5 $\log_{10}$ across cohorts
- Twenty-six of 34 subjects in these 5 cohorts had HBsAg < 100 IU/mL at some point during the study
- Eleven subjects in these cohorts were HBeAg-, HBV DNA <LLOQ, and HBsAg <100 IU/mL with ALT< 2xULN at least 24 weeks post last dose of AB-729 and qualified to discontinue NA therapy; 9 subjects have consented
  - NA discontinuation subjects are identified in the figures above by a masked subject ID consistent with the AB-729-001 NA discontinuation poster SAT448
- One subject in Cohort E (baseline HBsAg = 583.5 IU/mL) who qualified but declined to participate in NA discontinuation seroconverted at Week 84 (HBsAg < LLOQ and HBsAb = 189 mIU/mL at last visit); liver enzymes remained within normal limits.

Figure 3: Cohort K Change in HBsAg and HBeAg vs time



Note: Dashed vertical lines indicate a dosing visit; Last Dose of AB-729 Cohort K = Week 40

- HBsAg (panels A and B):
  - All subjects in Cohort K had HBsAg <100 IU/mL during AB-729 treatment or follow up
  - To date, two subjects have reached HBsAg <LLOQ at one or more visits
- HBeAg (panels C and D):
  - The mean (SE) $\log_{10}$ change from baseline in HBeAg at Week 48 was -0.94 (0.25) IU/mL
  - $\log_{10}$ change in HBeAg may have been limited by low baseline values (maximum HBeAg = 98.2 IU/mL)
  - One subject reached HBeAg <LLOQ and has remained near the LLOQ

Table 3: Adverse events and laboratory abnormalities

Subjects, n (%)	HBV DNA- Cohort E [N=7]	Cohort F [N=7]	Cohort I [N=6]	Cohort J [N=7]	Cohort K [N=7]	HBV DNA+ Cohort G [N=7]	TOTAL [N=41]
Subjects with any TEAE	4 (57)	5 (71)	1 (17)	3 (43)	5 (71)	5 (71)	23 (56)
Grade 1	3 (43)	4 (57)	0	2 (29)	4 (57)	4 (57)	17 (42)
Grade 2	1 (14)	1 (14)	1 (17)	1 (14)	1 (14)	0	5 (12)
Grade 3	0	0	0	0	0	1 (14)‡	2 (5)
SAEs (all unrelated)	0	0	0	1 (14)*	0	1 (14)‡	2 (5)
Subjects with related TEAEs (all Grade 1)	2 (29)	4 (57)	1 (17)	2 (29)	5 (71)	2 (29)	16 (39)
Most common related TEAEs (in ≥ 2 subjects):							
Injection site pain	0	2 (29)	0	1 (14)	4 (57)	1 (14)	9 (4)#
Injection site erythema	2 (29)	1 (14)	0	0	1 (14)	0	5 (2)#
Injection site bruising	2 (29)	0	1 (17)	0	0	0	3 (1)#
Liver–related laboratory abnormalities:							
ALT elevation							
Grade 2	2 (29)	1 (14)	2 (33)	0	3 (43)	1 (14)	9 (22)
Grade 3 or 4	0	0	0	0	0	0	0
AST elevation							
Grade 2	1 (14)	0	0	0	0	1 (14)	2 (5)
Grade 3 or 4	0	0	0	0	0	0	0

TEAE: treatment-emergent adverse event; SAE: serious adverse event; Grading criteria: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, V2.1
TEAE window was 12 weeks post-last dose of AB-729, data presented are cumulative from Screening/Study Day 1; worst grade of TEAE or lab abnormality reported
* SAE was an unrelated Grade 3 diagnosis of cholangiocarcinoma >12 weeks post last dose of AB-729; ‡ SAE was an unrelated Grade 3 thigh subcutaneous cyst abscess
# n, % is number of events out of 242 total AB-729 doses administered in Part 3

- 2 SAEs noted were both unrelated to AB-729 treatment:
  - Grade 3 cholangiocarcinoma diagnosed >4 months post-last dose of AB-729; subject withdrawn to undergo treatment
  - Grade 3 thigh subcutaneous cyst abscess required brief hospitalization for IV antibiotics; subject continued in the study
- Mild to moderate ALT elevations observed in DNA- CHB subjects undergoing AB-729 repeat dosing may be associated with HBV-specific T-cell IFN-γ production (see poster SAT397).

Safety Summary

- There were no deaths or treatment discontinuations due to AEs
- Two SAEs were observed, both were unrelated to AB-729 and did not impact AB-729 treatment
- The most common TEAEs related to AB-729 were injection site-related
  - All were Grade 1 and did not appear to be dose or interval dependent
- All ALT and AST elevations were Grade 2 or lower; all were asymptomatic and not considered AEs by the Investigators
  - ALT/AST elevations improved or stabilized with continued dosing
  - No bilirubin or liver synthetic function changes were seen
- No clinically significant changes in other laboratory results, ECGs, or vital signs were seen

CONCLUSIONS

- AB-729 repeat dosing continues to be generally safe and well tolerated.
- AB-729 provided a robust HBsAg decline in a cohort of only HBeAg+ subjects that was comparable to cohorts composed of mostly HBeAg- subjects which further demonstrates an absence of effect of HBeAg status on AB-729 treatment response.
  - Two subjects in Cohort K reached HBsAg <LLOQ at one or more visits
- Further follow-up of a dedicated DNA+ cohort (Cohort G) continues to demonstrate HBsAg response comparable to DNA- subjects.
- Overall, 11 of 32 subjects who completed 48 weeks of treatment and who were HBeAg-, HBV DNA <LLOQ, HBsAg <100 IU/mL with ALT< 2xULN at least 24 weeks post last dose of AB-729 and were given the opportunity to discontinue NA therapy [see poster SAT448].
- One subject in Cohort E who qualified for but chose not to discontinue NA became HBsAg <LLOQ and seroconverted at Week 40 post last dose of AB-729 with steadily increasing HBsAb (most recent = 189 mIU/mL).
- These data support the continued evaluation of AB-729 as the cornerstone of combination treatment to achieve functional cure of chronic HBV.

REFERENCES

[1]European Association for the Study of the Liver, EASL 2017 Clinical Practice Guidelines on the management of hepatitis B infection. J Hepatol, 2017. 67(2):370-398.
[2]Sarin SK, et al. Hepatol Int, 2016. 10(1):p:1-98.
[3]Terrault N, et al. Hepatol, 2018. 67(4)p:1560-1599.
[4]Yuen MF, et al. AASLD 2020, #83.
[5]Gane E, et al. EASL 2021, #PO2879.
[6]Yuen MF, et al. EASL 2021, #LBO2764.
[7]Yuen MF, et al. AASLD 2021, #LP20.

ACKNOWLEDGEMENTS

Arbutus Biopharma thanks all participating subjects and their families, the investigators and site staff, Novotech, LabCorp, PharStat Inc., Maks Chernyakhovskyy, and the AB-729 Research and Clinical Development Teams.

CONTACT INFORMATION AND DISCLOSURES

Timothy Eley, Ph.D., Executive Director, Compound Development Lead and Clinical Pharmacology
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA, USA 18974
Email: teley@arbutusbio.com
Tel: +1-267-422-1320

Authors affiliated with Arbutus Biopharma are employees and may own company stock.

www.arbutusbio.com