Low HBsAg levels maintained following cessation of the GalNAc-siRNA, AB-729, in chronic hepatitis B subjects on nucleos(t)ide analogue therapy

MF Yuen[1], E Berliba[2], W Sukeepaisarnjaroen[3], P Tangkijvanich[4], A Leerapun[5], J Holmes[6], E Gane[7], A Jucov[2], EP Thi[8], M Sofia[8], H Sevinsky[9], T Eley[9], E Medvedeva[9], K Gray[9], D Antoniello[9], G Picchio[9], KD Sims[9], SI Strasser[10]

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

AASLD The Liver Meeting® Nov. 12-15, 2021

LP20

Arbutus BIOPHARMA
Curing Chronic Hepatitis B

INTRODUCTION

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 HBV therapies that have the potential to provide a functional cure for CHB.

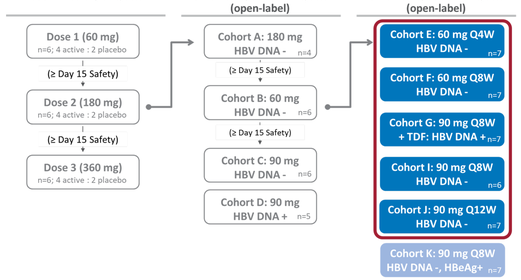
AB-729 is a subcutaneously administered *N*-Acetylgalactosamine (GalNAc)-conjugated single trigger pan-genotypic RNA interference therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens. AB-729 targets the liver via proprietary 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 AB-729. Safety and PD following single doses of AB-729 (Part 2 Cohorts A, B, C, D) in virologically-suppressed CHB subjects on nucleos(t)ide analogue (NA) therapy have been reported previously.[4,5,6]

Here we report additional safety and PD from repeat dose cohorts from study AB-729-001 beginning with initiation of treatment and up to 28 weeks post last dose of AB-729 in HBV DNA+ and DNA- CHB subjects.

METHODS

Figure 1: AB-729-001 Study Design



- Cohorts E, F, I, and J enrolled HBeAg positive and negative, HBV DNA- subjects on stable NA therapy.
- Cohort G enrolled HBeAg positive and negative, HBV DNA+ subjects who began treatment with TDF concurrently with AB-729.
- All 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; 33 of 34 eligible 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 AB-729 discontinuation.

RESULTS

Table 1: Baseline Characteristics

Baseline Measure#	HBV DNA- Cohort E‡ (N=7)	HBV DNA- Cohort F (N=7)	HBV DNA- Cohort I (N=6)^	HBV DNA- Cohort J (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)	43.9 (34 – 50)
Male gender, n (%)	4 (57%)	4 (57%)	4 (67%)	5 (71%)	3 (43%)
BMI, mean (SD)	27.7 (5.0)	23.7 (2.2)	25.5 (3.1)	28.7 (4.8)	23.8 (4.0)
Race, n (%)					
Asian	1 (14%)	5 (71%)	5 (83%)	4 (57%)	6 (86%)
Black	0	1 (14%)	0	0	0
White	6 (86%)	1 (14%)	1 (17%)	3 (43%)	1 (14%)
ALT (U/L), mean (SD)	22.4 (10.5)	23.4 (15.2)	26.0 (10.2)	20.1 (7.2)	32.7 (15.8)
HBV eAg negative, n (%)	7 (100%)	6 (71%)°	5 (83%)	4 (57%)	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)	1,818 (277 – 4,723)

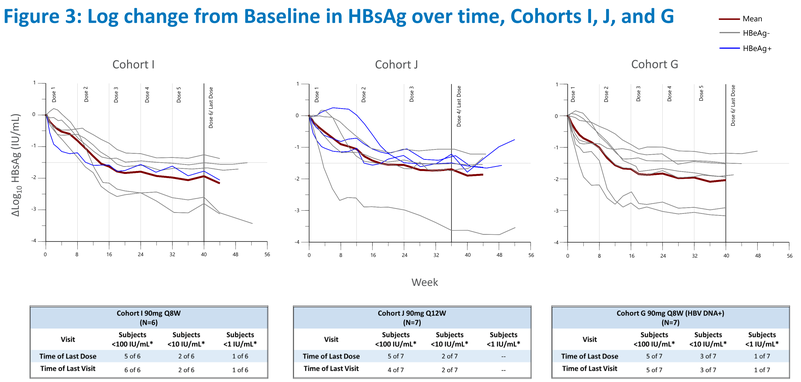
#Genotype not determined; ‡Subjects switched to AB-729 60 mg Q12W for the extension phase; ^N = 6 due to one subject meeting exclusion criteria on Day 1 and a replacement subject receiving an incorrect dose on Day 1; both entered follow up and were excluded from the analysis; ♦Mean (SD) Baseline Log10 HBV DNA = 3.88 (0.87); °One subject counted as HBeAg negative was identified as "HBeAg borderline" (baseline HBeAg = 0.18 IU/mL, LLOQ = 0.11 IU/mL)

Table 2: Mean (SE) Baseline and Δlog$_{10}$ HBsAg by Visit

Nominal Visit	HBV DNA- Cohort E (N=7)	HBV DNA- Cohort F (N=7)	HBV DNA- Cohort I (N=6)	HBV DNA- Cohort J (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)	3.14 (0.14)
Week 12	-1.10 (0.15)	-1.02 (0.11)	-1.30 (0.19)	-1.06 (0.31)	-1.56 (0.32)
Week 24	-1.84 (0.16)	-1.57 (0.09)	-1.79 (0.22)	-1.56 (0.25)	-1.82# (0.29)
Week 40	-1.84 (0.19)	-1.78 (0.10)	-1.93 (0.25)	-1.89◇ (0.35)	-2.03† (0.33)
Week 44	-1.81 (0.17)	-1.88 (0.13)	-2.16 (0.31)	-1.86◇ (0.38)	---
Week 48	-1.89 (0.18)	-1.90 (0.14)	---	---	---
Week 16 Post Last Dose	-1.74 (0.20)	-1.76 (0.19)	---	---	---
Week 20 Post Last Dose	-1.61 (0.20)	-1.55* (0.28)	---	---	---
Week 24 Post Last Dose	-1.54 (0.19)	---	---	---	---

NOTE: Mean (SE) values presented only if N>3; there are no statistically significant differences between cohorts (data not shown); *N = 5; ◇N = 6, one subject in Cohort J chose not to extend treatment; #6 of 7 subjects had HBV DNA <LLOQ by Week 8 and the 7th subject became <LLOQ at Week 16; †N = 6

Figure 3: Log change from Baseline in HBsAg over time, Cohorts I, J, and G



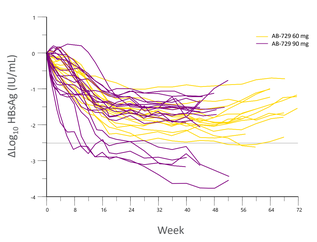
Cohort I 90mg Q8W (N=6)			
Visit	Subjects <100 IU/mL*	Subjects <10 IU/mL*	Subjects <1 IU/mL*
Time of Last Dose	5 of 6	2 of 6	1 of 6
Time of Last Visit	6 of 6	2 of 6	1 of 6

Cohort J 90mg Q12W (N=7)			
Visit	Subjects <100 IU/mL*	Subjects <10 IU/mL*	Subjects <1 IU/mL*
Time of Last Dose	5 of 7	2 of 7	--
Time of Last Visit	4 of 7	2 of 7	--

Cohort G 90mg Q8W (HBV DNA+) (N=7)			
Visit	Subjects <100 IU/mL*	Subjects <10 IU/mL*	Subjects <1 IU/mL*
Time of Last Dose	5 of 7	3 of 7	1 of 7
Time of Last Visit	5 of 7	3 of 7	1 of 7

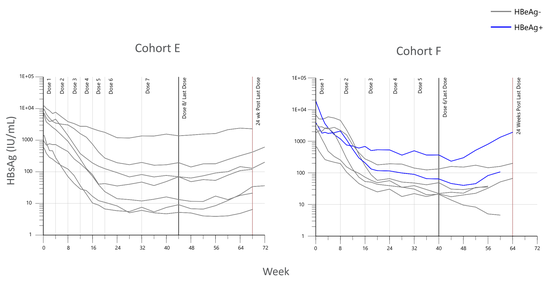
*At any time on treatment or during follow-up

Figure 4: Log change in HBsAg by dose



- Log change from baseline in HBsAg appears largely independent of dose
- A subset of subjects experiencing a >2.5 log response was identified:
  - All were HBeAg negative
  - 5/7 received AB-729 90 mg
  - 5/7 were female
  - 6/7 were Asian

Figure 5: Individual HBsAg over time, Cohorts E and F



Cohort E 60mg Q4W (N=7)			
Visit	Subjects <100 IU/mL*	Subjects <10 IU/mL*	Subjects <1 IU/mL*
Time of Last Dose	5 of 7	2 of 7	--
Time of Last Visit	3 of 7	1 of 7	--
24 Week Post Last Dose	3 of 7	1 of 7	--

Cohort F 60mg Q8W (N=7)			
Visit	Subjects <100 IU/mL*	Subjects <10 IU/mL*	Subjects <1 IU/mL*
Time of Last Dose	5 of 7	--	--
Time of Last Visit	4 of 7	1 of 7	--
24 Week Post Last Dose	1 of 3	--	--

*At any time on treatment or during follow-up

Table 3: Adverse Events and Lab Abnormalities

Subjects, n (%)	HBV DNA- Cohort E* [N=7]	HBV DNA- Cohort F [N=7]	HBV DNA- Cohort I [N=6]	HBV DNA- Cohort J [N=7]	HBV DNA+ Cohort G [N=7]	TOTAL [N=34]
Subjects with any TEAE	4 (57)	5 (71)	1 (17)	3 (43)	4 (57)	17 (50)
Grade 1	3 (43)	4 (57)	0	2 (29)	3 (43)	12 (35)
Grade 2	1 (14)	1 (14)	1 (17)	1 (14)	0	4 (12)
Grade 3	0	0	0	0	1 (14)‡	1 (3)
SAEs	0	0	0	0	1 (14)‡	1 (3)
Subjects with related TEAEs (all Grade 1)	2 (29)	4 (57)	1 (17)	2 (29)	1 (17)	10 (30)
Most common related TEAEs (in ≥ 2 subjects):						
Injection site pain	0	2 (29)	0	1 (14)	0	3 (1)#
Injection site erythema	2 (29)	1 (14)	0	0	0	4 (2)#
Injection site bruising	2 (29)	0	1 (17)	0	0	4 (2)#
Liver–related laboratory abnormalities:						
ALT elevation^						
Grade 1	2 (29)	3 (43)	3 (50)	3 (43)	3 (43)	14 (41)
Grade 2	2 (29)	1 (14)	2 (33)	0	1 (14)	6 (18)
AST elevation^						
Grade 1	1 (14)	3 (43)	2 (33)	0	2 (29)	8 (24)
Grade 2	1 (14)	0	0	0	1 (14)	2 (6)

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
*subjects in Cohort E were switched to AB-729 60 mg Q12W after the Week 20 dose; ^subject's highest abnormality grade shown
‡ SAE was an unrelated Grade 3 thigh abscess (not at an AB-729 injection site) that required hospitalization for intravenous antibiotics
# n, % is number of events out of 214 total AB-729 doses administered

Safety Summary

- There were no deaths or discontinuations due to AEs.
- There was one unrelated SAE of Grade 3 thigh abscess due to a sebaceous cyst (not at an AB-729 injection site) in Cohort G that resolved after IV antibiotic therapy.
- 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.
- ALT and AST elevations 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 ECGs or vital signs were seen.

CONCLUSIONS

- AB-729 repeat dosing continues to be generally safe and well tolerated.
- Robust mean declines (1.8 – 2.0 $\log_{10}$) in HBsAg were sustained with repeat dosing of AB-729 up to 48 weeks, with no statistically significant differences observed to date between dose and/or dosing intervals.
- Greater variability in response was observed with the 90 mg dose which warrants further investigation.
- HBsAg suppression at levels <100 IU/mL is maintained in some subjects up to 28 weeks following the last dose of AB-729.
  - Sustained HBsAg antigen responses <100 IU/mL warrant considering NA discontinuation strategies to assess the potential for functional cure.
- To date, limited data in HBeAg+ subjects do not appear to indicate a differential response; Cohort K, evaluating 90mg Q8W in HBeAg+ subjects only is ongoing.
- 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.
[5]Gane E, et al. APASL 2021.
[6]Yuen MF, et al. EASL 2021.

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

Timothy Eley, Ph.D., Executive Director, Compound Development Lead and Clinical Pharmacology
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA 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