IM-PROVE I: Characterization of chronic hepatitis B (CHB) subjects with functional cure or HBV DNA suppression after completion of imdusiran plus short courses of pegylated interferon alfa-2a (IFN) and discontinuation of nucleos(t)ide analogue (NA) therapy

Man-Fung Yuen[1], Ronald G. Nahass[2], Grace Lai-Hung Wong[3], Tatiana Burda[4], Tuan T. Nguyen[5], Young-Suk Lim[6], Wan-Long Chuang[7], Eugene R. Schiff[8], Kalyan Ram Bhamidimarri[9], Kevin Gray[10], Emily P. Thi[10], Christine L. Espiritu[10], Elina Medvedeva[10], Timothy Eley[10], Mark Anderson[11], Tiffany Fortney[11], Gavin Cloherty[11], Karen D. Sims[10]
[1]The University of Hong Kong, Queen Mary Hospital, Hong Kong, China, [2]ID Care, Hillsborough, NJ, United States, [3]Medical Data Analytics Centre (MDAC), Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China, [4]Arensia Exploratory Medicine, Chisinau, Moldova, [5]Research and Education, Inc, San Diego, CA, United States, [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Rep. of South, [7]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [8]University of Miami Miller School of Medicine, Miami, FL, United States, [9]Cleveland Clinic Florida, Weston, FL, United States, [10]Arbutus Biopharma, Warminster, PA, United States, [11]Abbott Laboratories, Infectious Disease Research, North Chicago, IL, United States

EASL CONGRESS 7-10 May 2025 Amsterdam, the Netherlands
THU-260

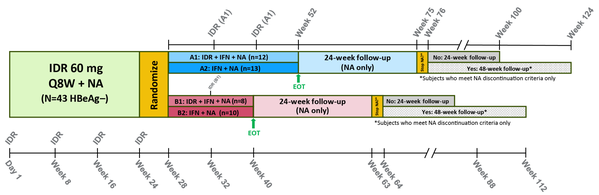
Arbutus BIOPHARMA
Curing Chronic Hepatitis B

BACKGROUND

- Functional cure of CHB (FC), defined as sustained HBV DNA <LLOQ and HBsAg loss for 24 weeks after HBV treatment cessation[1] is the current goal for most experimental treatment regimens being evaluated in clinical trials.
- Baseline (BL) characteristics of study subjects and HBV biomarker levels at key timepoints that may help predict likelihood of FC in subjects who complete finite courses of experimental treatment for CHB remain unclear.
  - Low levels of HBsAg at BL (specifically ≤1000 IU/mL) appear to be associated with increased HBsAg loss and FC rates[2-5], but other factors have not yet been identified
- The IM-PROVE I study was a Phase 2a proof-of-concept study in 43 NA-suppressed, HBeAg-negative CHB subjects who received 4 doses of imdusiran (IDR) (60 mg every 8 weeks) prior to randomization to 24 weeks or 12 weeks of IFN with or without additional imdusiran doses. Eligible subjects discontinued (d/c) NA therapy 24 weeks after end-of- IFN treatment.
- Six subjects in this study achieved functional cure after NA d/c; 3 additional subjects had HBV DNA <LLOQ with low HBsAg levels during NA d/c follow-up.
- Further characterization of these subjects including all available demographic and baseline characteristics, HBV treatment history, and additional HBV biomarkers are presented at key timepoints during the study.

MATERIALS AND METHODS

IM-PROVE I (AB-729-201) Study Design



- IM-PROVE I enrolled 43 non-cirrhotic, HBeAg-negative, virally suppressed CHB subjects on stable NA therapy for ≥12 months before Day 1
- All subjects received 24 weeks (4 doses) of IDR 60 mg every 8 weeks and were randomized at Week 24 into 1 of 4 groups (stratified by HBsAg level ≤100 or >100 IU/mL at Week 24):
  - Cohort A1: IDR ×2 doses + NA + weekly IFN (180 µg) for 24 weeks (n=12)
  - Cohort A2: NA + weekly IFN (180 µg) for 24 weeks (n=13)
  - Cohort B1: IDR ×1 dose + NA + weekly IFN (180 µg) for 12 weeks (n=8)
  - Cohort B2: NA + weekly IFN (180 µg) for 12 weeks (n=10)
- After the end of IFN treatment (EOT), subjects were followed for an additional 24 weeks on NA therapy alone and then assessed for NA discontinuation via the following criteria:
  - Alanine aminotransferase (ALT) <2 × upper limit of normal (ULN), undetectable HBV DNA, and HBsAg <100 IU/mL at 2 consecutive visits ≥24 weeks after the last dose of IDR
- Key inclusion/exclusion criteria have been presented previously[2]
- Study assay methods/cutoffs:
  - HBsAg was assessed with Elecsys® HBsAg II quant II (Roche Diagnostics); LLOQ = 0.05 IU/mL
    - HBsAg loss is defined as ≤LLOQ as determined via Roche assay
    - HBsAg results below the LLOQ via Roche assay were also analyzed by ARCHITECT HBsAg Next Qualitative Assay (Abbott Diagnostics); lower limit of detection (LLOD) = 0.005 IU/mL[5]
  - HBV DNA was assessed with cobas® HBV Test 6800 (Roche Diagnostics); LLOQ = 10 IU/mL
  - Hepatitis B core-related antigen (HBcrAg) was assessed with Fujirebio Lumipulse G; LLOQ = 1.0 kU/mL
  - HBV RNA was assessed via Abbott v2.0 RUO assay; LLOQ = 0.49 $\log_{10}$ U/mL or 3.0 U/mL
  - Anti-HBs was assessed with Elecsys® Anti-HBs II (Roche Diagnostics); LLOQ = 2.0/3.5 IU/L
  - ALT ULN = 41 U/L for males and 33 U/L for females
  - IL28b genotype (rs12979860) was assessed via AccuType IL28B (Quest Diagnostics)
  - HBV genotype was assessed via ultradeep sequencing of region spanning HBsAg/Pol[7]. Samples unable to be sequenced were serotyped with IMMUNIS® HBV Genotype EIA

RESULTS

Table 1: Baseline characteristics of key study subjects

- Subjects with FC were defined as sustained HBV DNA <LLOQ and HBsAg loss for 24 weeks after NA discontinuation
  - 5 subjects from Cohorts A1/A2 and 1 subject from Cohort B2 all maintained FC status through the end of study visit (at least 46 weeks after NA discontinuation)
- Subjects with sustained HBV DNA suppression after NA discontinuation were defined as HBV DNA <LLOQ for at least 12 weeks while off NA therapy (transient "blips" were permitted) with detectable HBsAg (akin to early partial cure[1])
  - Subject 31 (A1): HBV DNA <LLOQ from time of NA d/c (Week 77) through EOS (Week 124) with transient "blip" to 128 IU/mL at Week 86
  - Subject 20 (B1): HBV DNA <LLOQ from time of NA d/c (Week 65) through EOS (Week 112) with transient "blips" to 258 IU/mL at Week 76, 24 IU/mL (Week 88) and 19 IU/mL (Week 100)
  - Subject 4 (B2): HBV DNA <LLOQ from time of NA d/c (Week 65) to Week 96 with rebound to 49,400 IU/mL (Week 76) and spontaneous re-suppression (Week 79), "blip" to 94 IU/mL at Week 108
- Subjects with transient HBsAg loss were defined as having sustained HBsAg <LLOQ for at least consecutive 12 weeks prior to seroreversion

	Functional Cure						HBV DNA suppression			Transient HBsAg loss		Study totals (N=43)
	Subject 40	Subject 23	Subject 16	Subject 3	Subject 35	Subject 12	Subject 31	Subject 20	Subject 4	Subject 13	Subject 1	
Cohort	A1	A1	A1	A2	A2	B2	A1	B1	B2	A1	A2	All
Gender	F	F	M	F	M	M	M	M	M	F	M	Males: 31 (72%)
Age (y)	50	52	55	49	54	48	43	53	49	47	38	Median: 47.0
Race	Asian	Asian	Asian	Asian	White	Asian	Asian	Pacific Islander/Hawaiian	Asian	Asian	Asian	Asian: 34 (79%) White: 7 (16%)
Country	Hong Kong	US	South Korea	Hong Kong	US	US	Taiwan	Moldova	US	Hong Kong	Taiwan	-
Year of HBV diagnosis	2006	2015	1995	2005	1972	UNK (>2009)	2014	2015	2008	2009	2015	Median: 2006 Range: 1972-2020
Current background NA therapy (years)	ETV (7)	TAF (2)	TAF (5)	TDF (5)	TAF (6)	TDF (12)	TAF (6)	TDF (4)	TDF (15)	ETV (7)	ETV (4)	ETV: 13 (30.2%) TDF: 16 (37.2%) TAF: 14 (32.6%)
Total duration of NA treatment (years)	7	2	17	18	UNK (6+)	15	9	4	16	7	8	Mean: 9.11 (SD 5.7) Median: 7
HBV GT	C	B	C	B	A	A	B	D	C	B	B	A: 9%, B: 33% C: 44%
IL28b GT (rs12979860)	C/C	C/C	C/C	C/C	C/T	C/C	C/C	UNK	C/C	C/C	C/C	C/C: 60.5% C/T: 20.9% T/T: 2.3% UNK: 16.3%
IFN dose modification	N	Y – neutropenia & ALT (reduced x 4 doses, held x 6 doses)	N	Y – neutropenia (held x 17 doses)	N	N	N	N	N	N	N	Y: 9/43 (20.9%)

abbreviations: ETV = entecavir, TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UNK = unknown; IL28b = interleukin 28b; GT = genotype; ALT – alanine aminotransferase

- No baseline characteristics appeared to strongly correlate with functional cure or other outcomes, but the FC subjects appeared to have a longer total duration of NA treatment

Table 2: HBV biomarkers at key study timepoints

	Functional Cure						HBV DNA suppression			Transient HBsAg loss		Study Totals (N=43)
	Subject 40	Subject 23	Subject 16	Subject 3	Subject 35	Subject 12	Subject 31	Subject 20	Subject 4	Subject 13	Subject 1	
Cohort	A1	A1	A1	A2	A2	B2	A1	B1	B2	A1	A2	All
HBsAg (IU/mL)												
Baseline	129.1	576.3	492.3	355.5	68.8	1186	1325	603	712	639.2	1228	BL Mean: 1555 (SD 1437) Median: 825 Range: 47.6 – 5109
At NA d/c	0.05	<0.05	<0.05	<0.05	<0.05	37.35	81.35	55.6	11.74	<0.05	N/A (277.7)	
Next Assay neg at NA d/c	Y	Y	Y	Y	Y	N	N/A	N/A	N/A	Y	N/A	
Timing of HBsAg loss	Week 48	Week 48	Week 44	Week 44	Week 44	Week 88	Week 56	N/A (nadir 24.3 at Week 28)	N/A (nadir 2.11 at EOS)	Week 44	Week 44	
Timing of relapse†	N/A	N/A	N/A	N/A	N/A	N/A	Week 60	-	-	Week 86	Week 60	
HBsAb (mIU/mL)												
Baseline	<2.0	2.0	<2.0	<2.0	2.0	<2.0	41.7	<2.0	<2.0	<2.0	<2.0	N/A
At NA d/c	26.1	247.7	50.1	398.3	163.3	<2.0	143.3	<2.0	<2.0	39.9	<2.0	
Maximum	43.8	247.7	149.5	401.4	>1000	<2.0	444.6	<2.0	<2.0	366.4	<2.0	
HBV RNA (U/mL)												
Baseline	19.95	478.6	<LLOQ	9.12	30.9	11.48	40.74	TND	8.13	616.59	9.77	BL Mean: 64.9 (SD 127.4) Median: 21.9
At NA d/c	TND	8.31	TND	<LLOQ	-	TND	15.14	TND	TND	TND*	11.75	
HBcrAg (kU/mL)												
Baseline	<1.0	<1.0	8.4	<1.0	<1.0	<1.0	196	<1.0	<1.0	1.3	3.0	BL Mean: 12.68 (SD 33.83) Median: 1.5
At NA d/c	<1.0	1.1	4.8	<1.0	<1.0	<1.0	53.3	<1.0	<1.0	<1.0	1.5	
ALT (U/L)												
Maximum ALT	25 (Gr 0)	216 (Gr 3)	68 (Gr 1)	105 (Gr 2)	101 (Gr 1)	148 (Gr 2)	94 (Gr 1)	137 (Gr 2)	148 (Gr 2)	59 (Gr 1)	124 (Gr 2)	Gr 3 ALT: 5 subjects (max 256; Week 4 – 40)
Time of maximal ALT	Week 34	Week 32 (IFN dose adj)	Week 40	Week 32	Week 38	Week 30	Week 32	Week 32	Week 30	Week 36	Week 32	

abbreviations: BL = baseline; NA = nucleos(t)ide analogue; d/c = discontinuation; N/A = not applicable; TND – target not detected; Gr = Grade (DAIDS); adj = adjustment; †relapse defined as HBsAg >LLOQ; *Week 78

- HBsAg <1000 IU/mL at BL and HBsAg <LLOQ at the time of NA discontinuation were more common amongst FC subjects
- Next Assay results at the NA d/c timepoint did not uniformly correlate with maintenance of HBsAg loss and FC, but Subject 13 reverted to a positive Next Assay result at Week 68 (18 weeks prior to reversion of the standard HBsAg assay) suggesting that the Next Assay may be useful as an early predictor of seroreversion; Subject 1 never achieved a negative Next Assay result despite prolonged HBsAg loss and did not achieve FC
- HBcrAg was <LLOQ at BL in all but 1 FC subject, but was also <LLOQ in several subjects that did not achieve FC; HBV RNA and anti-HBs levels also did not appear to correlate with FC
- Significant ALT "flares" were not necessary to achieve FC, and IFN dose modifications due to ALT elevations or neutropenia did not appear to impact results

CONCLUSIONS

- Functional cure rates in IM-PROVE I were highest amongst subjects who received 6 doses of imdusiran (60 mg every 8 weeks) and 24 weeks of weekly IFN starting at Week 28, compared to those that received shorter courses of imdusiran (4 doses) and/or IFN (12 weeks)
- Type of NA therapy (tenofovir-based vs entecavir) did not appear to impact likelihood of FC or predict relapse after NA discontinuation
- Higher FC rates may be associated with longer time on NA therapy prior to study enrollment, but more data are needed
- IFN dose modifications (reductions or interruptions) due to ALT elevations or neutropenia did not appear to impact achievement of FC
- Higher FC rates were observed in subjects with baseline HBsAg <1000 IU/mL
  - HBsAg <LLOQ at the time of NA discontinuation was more common in subjects that went on to FC
  - In the 5 FC subjects who received 24 weeks of IFN, a sharp decline in HBsAg to <LLOQ was observed after ~12-14 weeks of IFN treatment
- A positive Next Assay result (HBsAg LLOD of 0.005 IU/mL vs 0.05 IU/mL) was a very early predictor of seroreversion (Subject 13, 18 weeks prior to standard assay reversion), and predicted subjects who did not maintain durable HBsAg loss (Subject 1) despite sustained <LLOQ via standard assay
- Significant ALT flares were not observed in the subjects that achieved FC, although IFN treatment led to asymptomatic Gr 1 to Gr 3 ALT elevations in several subjects across the study cohorts
- Other HBV biomarkers including HBcrAg, HBV RNA and anti-HBs did not appear to have strong predictive value for FC
- A larger dataset is needed to further explore the predictive value of subject characteristics and HBV-related biomarkers for FC
- Please see Poster THU-253 for additional IM-PROVE I exploratory HBV and immunology data

REFERENCES

[1] Ghany, M., et al., Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. J Hepatol, 2023. 79:p. 1254–1269.
[2] Yuen, M.F., et al., IM-PROVE I: Imdusiran in Combination with Short Courses of Pegylated Interferon Alfa-2a in Virally Suppressed, HBeAg-Negative Subjects with Chronic HBV (CHB) Infection Leads to Functional Cure. Hepatology 2025. 81(2):p. E44-E98.
[3] Hou, J., et al., Xalnesiran with or without an Immunomodulator in Chronic Hepatitis B. N Engl J Med, 2024. 391:p. 2098-2109
[4] Yuen, M.F., et al., Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection. N Engl J Med, 2022. 387:p. 1957-1968.
[5] Gane, E., et al., Tobevibart (Vir-3434) and Elebsiran (Vir-2218) with or without Pegylated Interferon Alfa-2a for the Treatment of Chronic HBV Infection: End Of Treatment Results after 48 Weeks of Therapy (March Study). Hepatology, 2025. 81(2):p. E44-E98.
[6] Anderson, M. et al. Ultrasensitive HBsAg testing predicts HBsAg seroreversion outcomes: considerations for new and existing therapies. J Hepatol, 2024. 81 (1):e24-e25.
[7] Liu et al. Developing a sensitive HBV genotyping assay for HBV DNA suppressed patients using both DNA and RNA sequencingJ Med Virol. 2020; 92:3420-3425.

ACKNOWLEDGEMENTS

Arbutus Biopharma thanks all participating subjects and their families, the IM-PROVE I Investigators and site staff, Novotech CRO and ProTrials Research, Q² Solutions, Maksym Chernyakhovskyy and Crystal Grant for data management assistance, and the imdusiran Research and Development Teams.

CONTACT INFORMATION

Timothy Eley, PhD
Vice President, Clinical Pharmacology
Arbutus Biopharma
701 Veterans Circle
Warminster, PA 18974
www.arbutusbio.com
Email: teley@arbutusbio.com

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