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

Man-Fung Yuen,[1] Jeong J.H. Heo,[2] Ronald G. Nahass,[3] Grace Wong,[4] Tatiana Burda,[5] Eugene Schiff,[6] Tsung-Hui Hu,[7] Tuan Nguyen,[8] Chi-Yi Chen,[9] Young-Suk Lim,[10] Stuart C. Gordon,[11] Jacinta Holmes,[12] Wan-Long Chuang,[13] Naim Alkhouri,[14] Anita Kohli,[14] Kalyan Ram Bhamidimarri,[15] Kevin Gray,[16] Emily P. Thi,[16] Elina Medvedeva,[16] Timothy Eley,[16] Christine Espiritu,[16] Sharie C. Ganchua,[16] Christina Iott,[16] Mark Anderson,[17] Tiffany Fortney,[17] Gavin Cloherty,[17] Gaston Picchio,[16] Karen D. Sims[16]

[1]The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [2]Department of Internal Medicine, College of Medicine, Pusan National University Hospital, Busan, Republic of Korea; [3]ID Care, Hillsborough, NJ, USA; [4]The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; [5]Arensia Exploratory Medicine, Chisinau, Moldova; [6]University of Miami, Miller School of Medicine, Schiff Center for Liver Diseases, Miami, FL, USA; [7]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [8]Research and Education Inc, San Diego, CA, USA; [9]Chia-Yi Christian Hospital, Chia-Yi City, Taiwan; [10]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [11]Henry Ford Hospital, Detroit, MI, USA; [12]St. Vincent's University Hospital, Melbourne, Australia; [13]Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [14]Arizona Liver Health, Chandler, AZ, USA; [15]University of Miami, Miller School of Medicine, Miami, FL, USA; [16]Arbutus Biopharma, Warminster, PA, USA; [17]Abbott Laboratories, Abbott Diagnostics, Infectious Disease Research, Abbott Park, IL, USA

AASLD The Liver Meeting® Nov. 15–19, 2024 5036

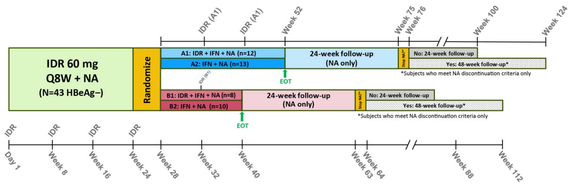
Arbutus BIOPHARMA *Curing Chronic Hepatitis B*

BACKGROUND

- Current therapies for chronic hepatitis B (CHB), including nucleos(t)ide analogues (NAs) or pegylated interferon alfa-2a (IFN), slow or prevent the development of hepatitis B virus (HBV)–related liver complications but typically lead to low rates of functional cure (FC, defined as sustained hepatitis B surface antigen [HBsAg] loss and HBV DNA less than the lower limit of quantification [LLOQ] 24 weeks off treatment, with or without hepatitis B surface antibodies [anti-HBs])[1-3]
- Excess production of HBsAg is believed to contribute to host immune exhaustion, resulting in inadequate T-cell and B-cell responses to CHB infection and failure to suppress the virus[4]; therefore, by lowering production of HBsAg and other viral antigens, suppressing viral replication, and restoring the anti-HBV host immune response, FC may be achieved[1]
  - Recent clinical trials testing experimental combinations have shown higher rates of HBsAg loss after NA cessation among those with low baseline HBsAg levels (<3000 IU/mL)[5-7]
- Imdusiran (IDR; AB-729) is a subcutaneously administered *N*-Acetylgalactosamine–conjugated, single trigger, pan-genotypic small interfering RNA therapeutic that blocks all HBV RNA transcripts, including HBV X protein, resulting in suppression of viral replication and all viral antigens,[8] and increases in HBV-specific immune responses in some subjects[9]
- The IM-PROVE I study (AB-729-201; NCT04980482) is an ongoing, randomized, open-label, multicenter phase 2a study assessing the safety, tolerability, and antiviral activity of 24 weeks (4 doses) of imdusiran followed by 12 or 24 weeks of IFN with or without additional imdusiran doses in virally suppressed, hepatitis B e-antigen (HBeAg) negative CHB subjects
  - We have previously shown that a 24-week course of IFN therapy in the context of profound suppression of HBsAg and viral replication by imdusiran + NA leads to sustained HBsAg loss in a subset of subjects through 24 weeks post-IFN treatment[9]
  - All available post-treatment follow-up data through the FC time point (24 weeks off all therapy) are presented

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[9]
- Study assay methods/cutoffs:
  - HBsAg was assessed with Elecsys® HBsAg II quant II (Roche Diagnostics); LLOQ = 0.05 IU/mL
  - HBsAg results found below the LLOQ via Roche assay were also analyzed by ARCHITECT HBsAg Next Qualitative Assay (Abbott Diagnostics); lower limit of detection = 0.005 IU/mL[10]
    - HBsAg loss is defined as ≤LLOQ as determined via Roche assay
  - HBV DNA was assessed with Cobas® HBV Test 6800 (Roche Diagnostics); LLOQ = 10 IU/mL[10]
  - Anti-HBs was assessed with Elecsys® Anti-HBs II (Roche Diagnostics); LLOQ = 10 IU/L
  - ALT ULN = 41 U/L for males and 33 U/L for females

RESULTS

Table 1. Demographics and Baseline Characteristics

Parameter	A1: IDR (6 doses) + NA + IFN 24W N=12	A2: IDR (4 doses) + NA + IFN 24W N=13	B1: IDR (5 doses) + NA + IFN 12W N=8	B2: IDR (4 doses) + NA + IFN 12W N=10	Total N=43
Age, mean (SD), y	45.5 (7.5)	41.5 (6.1)	48.6 (4.8)	47.2 (4.2)	45.3 (6.4)
Males, n (%)	6 (50)	12 (92)	6 (75)	7 (70)	31 (72)
Race, n (%)					
Asian	10 (83)	9 (69)	7 (88)	8 (80)	34 (79)
White	2 (17)	3 (23)	0	2 (20)	7 (16)
Other[a]	0	1 (8)	1 (12)	0	2 (5)
ALT, mean (SD), U/L	19.2 (6.1)	25.3 (9.8)	30.0 (13.2)	25.8 (11.0)	24.6 (10.3)
HBsAg, IU/mL					
Mean (SD)	1621 (1522)	1366 (1189)	1252 (1491)	1964 (1691)	1555 (1437)
<1000 IU/mL, n (%)	6 (50)	7 (54)	6 (75)	4 (40)	23 (54)
Range	129-4545	69-3070	455-4870	48-5109	48-5109
HBV genotype, n (%)					
A/E	0	1 (8) [E]	0	1 (10) [A]	2 (5)
B	3 (25)	2 (15)	2 (25)	1 (10)	8 (19)
C	4 (33)	2 (15)	4 (50)	3 (30)	13 (30)
D	1 (8)	0	0	1 (10)	2 (5)
Not determined	4 (33)	8 (62)	2 (25)	4 (40)	18 (42)

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IDR, imdusiran; IFN, pegylated interferon alfa-2a; NA, nucleos(t)ide analogue; W, weeks. [a]Black or African American (n=1); Native Hawaiian or other Pacific Islander (n=1).

- Cohorts were generally well balanced; most subjects were male, identified as Asian, and had HBV genotype B or C, with mean HBsAg >1000 IU/mL

On-Treatment Safety Summary

- The combination of imdusiran and IFN was well tolerated, with adverse events (AEs) being primarily Grade 1 or 2, as previously reported[9]
  - No related serious AEs, no Grade 4 AEs, and no study discontinuations due to AEs were reported
- Most Grade 3 AEs were laboratory abnormalities related to IFN, including decreased neutrophil count and ALT elevation
- Discontinuation of NA therapy in 21 of the 43 study subjects has also been well tolerated
  - 5/21 subjects who discontinued NA therapy have restarted NA treatment (2 per investigator request, 3 per protocol criteria of confirmed HBV DNA >20,000 IU/mL)
  - Only 1 subject experienced an accompanying ALT elevation at the time of NA restart (Grade 2 at the time of restart which increased to Grade 4 two weeks after restart, then improved)

Figure 1. Individual Subject HBsAg Levels by Cohort Over Time

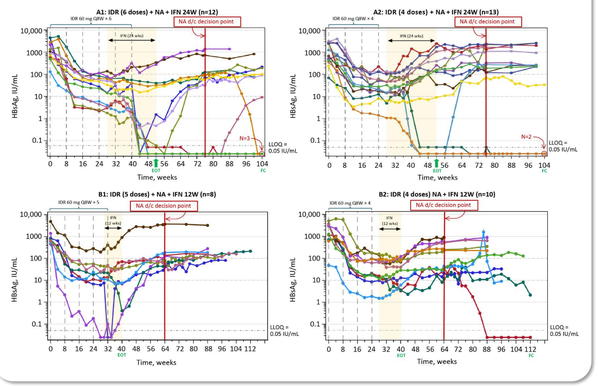


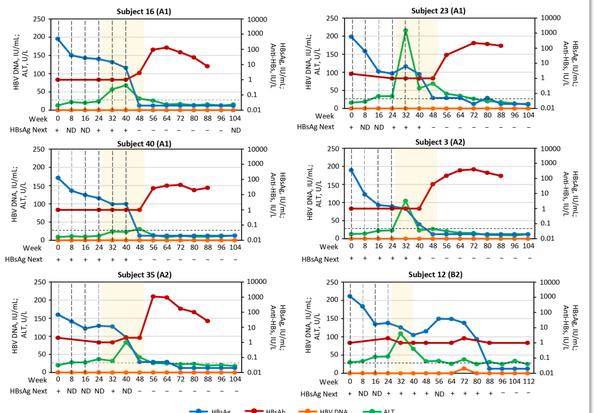
Table 2. Subjects With HBsAg Loss at Key Time Points

Achieved HBsAg loss (≤0.05 IU/mL) at time point, n/N (%)	A1: IDR (6 doses) + NA + IFN 24W N=12	A2: IDR (4 doses) + NA + IFN 24W N=13	B1: IDR (5 doses) + NA + IFN 12W N=8	B2: IDR (4 doses) + NA + IFN 12W N=10
EOT				
All	4/12 (33)	3/13 (23)	0/8	0/10
BL HBsAg <1000 IU/mL	4/6 (67)	2/7 (29)	0/6	0/4
24W Post-EOT				
All	4/12 (33)	2/13 (15)	0/8	0/10
BL HBsAg <1000 IU/mL	4/6 (67)	2/7 (29)	0/6	0/4
FC				
All	3/12 (25)	2/13 (15)	0/8	1/10 (10)
BL HBsAg <1000 IU/mL	3/6 (50)	2/7 (29)	0/6	0/4

BL, baseline; EOT, end of IFN treatment; FC, functional cure; HBsAg, hepatitis B surface antigen; IDR, imdusiran; IFN, pegylated interferon alfa-2a; NA, nucleos(t)ide analogue; W, week.

- Treatment with IFN for 24 vs 12 weeks and the continuation of imdusiran during IFN treatment led to greater HBsAg declines and more subjects reaching and maintaining HBsAg loss and achieving functional cure
- In Cohort A1/A2 subjects with baseline HBsAg <1000 IU/mL, sustained HBsAg loss at 24 weeks post-EOT was observed in 67% (4/6) in Cohort A1 and 29% (2/7) in Cohort A2
  - 5 of these 6 subjects achieved FC, resulting in an FC rate of 50% (3/6) in Cohort A1 and 29% (2/7) in Cohort A2
- One Cohort B2 subject also achieved FC during the NA discontinuation period and remained Abbott HBsAg Next assay negative at study completion

Figure 2. Individual Subject HBsAg (Standard and Ultrasensitive Assays), HBV DNA, Anti-HBs, and ALT Over Time in Subjects Who Achieved Functional Cure



Yellow shading indicates IFN treatment period. Vertical dashed lines indicate timing of IDR dosing. The horizontal dashed line indicates HBsAg LLOQ (0.05 IU/mL). ND, not done.

- Rapid HBsAg decline was observed during the imdusiran lead-in period in all subjects, with a second phase of HBsAg decline during the 24-week IFN treatment period
- For most subjects, anti-HBs levels increased as HBsAg became <LLOQ
- Abbott HBsAg Next Assay results became negative simultaneously or shortly after HBsAg reached <LLOQ as determined via Roche Assay
  - One Cohort A1 subject maintained HBsAg loss from EOT to 24 weeks post-EOT but then rebounded at Week 84; the Abbott HBsAg Next Assay result turned positive at Week 68, 16 weeks before seroreversion as determined via the Roche assay

CONCLUSIONS

- 4 or 6 doses of imdusiran plus 24 weeks of IFN was well tolerated and led to functional cure in 25% (3/12) of Cohort A1 subjects and 15% (2/13) of Cohort A2 subjects
- Subjects with baseline HBsAg <1000 IU/mL responded more favorably to the treatment regimens, with functional cure rates of 50% in Cohort A1
- The additional 2 doses of IDR administered during the 24 weeks of IFN treatment may improve functional cure rates
- The Abbott HBsAg Next Assay may be useful in predicting HBsAg seroreversion and should be evaluated in larger study populations
- These results demonstrate that achieving functional cure in HBV is possible with a finite treatment regimen
- Evaluation of IDR plus 24 weeks of IFN treatment in a larger confirmatory study is warranted
- Please see our other AASLD imdusiran presentations:
  - FRI poster 1383: IM-PROVE I Soluble Immune Biomarker Profiling
  - FRI poster 1391: Imdusiran Target Site Conservation
  - Late-breaker poster 5025: IM-PROVE II Preliminary Data With Nivolumab

ACKNOWLEDGEMENTS

Arbutus Biopharma thanks all participating subjects and their families, the investigators and site staff, Novotech CRO and ProTrials Research, Q2 Solutions, Lester Gibbs (Arbutus) for study support, Maksym Chernyakhovskyy (Arbutus) and Crystal Grant (Arbutus) for data management assistance, and the imdusiran (AB-729) Research and Development Teams. The IM-PROVE I study was sponsored by Arbutus Biopharma. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by Arbutus Biopharma.

REFERENCES

[1]EASL. *J Hepatol*. 2017;67:370-398.
[2]Sarin et al. *Hepatol Int*. 2016;10:1-98.
[3]Terrault et al. *Hepatology*. 2018;67:1560-1599.
[4]Yuen et al. *Nat Rev Dis Primers*. 2018;4:18035.
[5]Hou et al. EASL 2024; Milan, Italy. Oral presentation OS-030.
[6]Gane et al. The Liver Meeting® 2023; Boston, MA. Poster 5013-C.
[7]Yuen et al. *N Engl J Med*. 2022;387:1957-1968.
[8]Thi et al. *ACS Infect Dis*. 2024;10:3640-3649.
[9]Yuen et al. EASL 2024; Milan, Italy. Poster WED-371.
[10]Anderson et al. *J Hepatol*. 2024;81:e24-e25.

CONTACT INFORMATION AND DISCLOSURES

Corresponding Author: Karen Sims, MD, PhD
Chief Medical Officer
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA 18974
Email: ksims@arbutusbio.com

Man-Fung Yuen has received consulting fees from AbbVie, Abbott Diagnotics, Aligos Therapeutics, AiCuris, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GSK, Gilead Sciences, Immunocore, Janssen, Precision BioSciences, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology, and Visirna Therapeutics; and has participated on data safety monitoring boards or advisory boards for Aligos Therapeutics and Suzhou Ribo Life Science Co.

www.arbutusbio.com