Imdusiran (AB-729) administered every 8 weeks in combination with 24 weeks of pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection leads to HBsAg loss in some subjects at end of IFN treatment

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EASL CONGRESS Milan, Italy 5–8 June 2024 WED-371

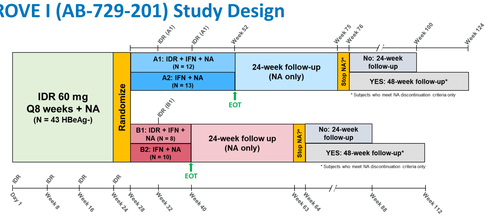
Arbutus BIOPHARMA *Curing Chronic Hepatitis B*

BACKGROUND

- Current therapies for chronic hepatitis B (CHB) including nucleos(t)ide analogues [NA] or pegylated interferon alfa-2a [IFN] slow or prevent the development of HBV-related liver complications, but typically lead to low rates of functional cure.[1,2,3]
- 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]. By lowering HBsAg and other viral antigen production, suppressing viral replication, and restoring the anti-HBV host immune response, functional cure may be achieved.
- Imdusiran (IDR; AB-729) is a subcutaneously administered *N*-Acetylgalactosamine (GalNAc)-conjugated, single trigger, pan-genotypic siRNA therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens.
- Given the immunostimulatory and HBsAg-lowering effects of IFN, a short pulse of therapy in the context of profound suppression of HBsAg and viral replication by imdusiran + NA may promote immune re-awakening and potentially lead to functional cure.
- 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 of IDR followed by 12 or 24 weeks of IFN with or without additional IDR doses in virally suppressed, HBeAg-negative CHB subjects. End of IFN treatment (EOT) data, 24-week post-EOT data and preliminary NA discontinuation data is presented (data cut April 23, 2024).

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 at least 12 months prior to Day 1
- All subjects received 24 weeks (4 doses) of imdusiran 60 mg every 8 weeks (Q8W) and were randomized at Week 24 into one of 4 groups (stratified by HBsAg level ≤100 or >100 IU/mL at Week 24):
  - A1: imdusiran + NA + weekly Peg-IFNα-2a (180 mcg) for 24 weeks (N = 12)
  - A2: NA + weekly Peg-IFNα-2a (180 mcg) for 24 weeks (N = 13)
  - B1: imdusiran + NA + weekly Peg-IFNα-2a (180 mcg) for 12 weeks (N = 8)
  - B2: NA + weekly Peg-IFNα-2a (180 mcg) for 12 weeks (N = 10)
- After completion of the IFN treatment period (EOT), subjects were followed for an additional 24 weeks on NA therapy alone, then assessed for NA discontinuation via the following criteria:
  - ALT <2× ULN, undetectable HBV DNA, and HBsAg <100 IU/mL at two consecutive visits at least 24 weeks after the last dose of imdusiran
- Key inclusion/exclusion criteria:

Inclusion:
- Males and females 18-60 years of age
- HBsAg between 100 – 5,000 IU/mL
- HBV DNA < lower limit of quantitation (LLOQ)
- Fibroscan ≤8.5 kPa within 6 months of Day 1

Exclusion:
- Coinfection with HDV, HIV or HCV
- ALT > 2× upper limit of normal (ULN)
- Direct or total bilirubin > 1.5× ULN
- Neutrophils <1500 cells/mm^3, platelets <150,000 cells/mm^3

- Study assay methods/cutoffs:
  - HBsAg was assessed with Roche Cobas Elecsys, LLOQ = 0.05 IU/mL;
  - HBsAg results <LLOQ via Roche assay were also analyzed by Abbott HBsAg Next Qualitative assay, LLOD = 0.005 IU/mL[5]
    - Undetectable HBsAg is defined as <LLOQ/LLOD via either HBsAg assay
  - HBV DNA was assessed with Roche Cobas 6800, LLOQ = 10 IU/mL
  - Anti-HBs antibody was assessed with Roche Cobas Elecsys e411/801, LLOQ = 10 mIU/mL
  - ALT upper limit of normal (ULN) = 41 U/L for males, 33 U/L for females
  - Biomarker profiling performed via 41- and 17-panel MILLIPLEX and Luminex xMAP INTELLIFLEX

RESULTS

Table 1: Demographic and Baseline Characteristics

Parameter	Cohort A1: IDR x 6 + NA + IFN x 24W (N = 12)	Cohort A2: IDR x 4 + NA + IFN x 24W (N = 13)	Cohort B1: IDR x 5 + NA + IFN x 12W (N = 8)	Cohort B2: IDR x 4 + NA + IFN x 12W (N = 10)	Study Total (N =43)
Age, Mean (SD)	45.5 (7.53)	41.5 (6.05)	48.6 (4.81)	47.2 (4.21)	45.3 (6.36)
Males, n (%)	5 (50)	12 (92.3)	6 (75)	7 (70)	31 (72.1)
Race, n (%)					
Asian	10 (83.3)	9 (69.2)	7 (87.5)	8 (80.0)	34 (79.1)
White	2 (16.7)	3 (23.1)	0	2 (20.0)	7 (16.3)
Other	0	1 (7.7)	1 (12.5)	0	2 (4.6)
ALT, Mean (SD)	19.17 (6.073)	25.31 (9.810)	30.00 (13.24)	25.80 (10.99)	24.58 (10.33)
HBsAg (IU/mL)					
Mean	1621	1366	1252	1964	1555
Range	(129.1 - 4545)	(68.8 – 3070)	(454.6 – 4870)	(47.6 – 5109)	(47.6 – 5109)
N (%) <1000 IU/mL	6 (50)	7 (54)	6 (75)	4 (40)	23 (54)
HBV genotype, n (%)					
A/E	0	1 [E]	0	1 [A]	2 (4.7)
B	3	2	2	1	8 (18.5)
C	4	2	4	3	13 (30.2)
D	1	0	0	1	2 (4.7)
Not typable	4	8	2	4	18 (41.9)

IDR: imdusiran; NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; W: weeks; ALT: alanine aminotransferase

- Cohorts were well-balanced, mostly male, Asian, HBV genotype B or C, with mean HBsAg >1000 IU/mL

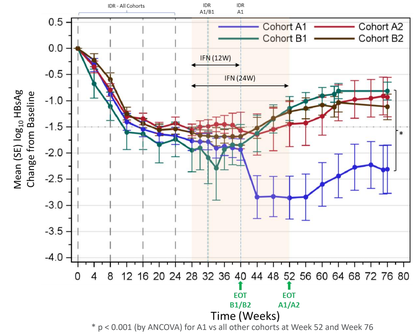
Table 2: On-Treatment Safety Summary

Subjects, N (%)	Study Treatment Period: IDR 24W Lead-In (N=43)	Cohort A1: IDR + NA + IFN x 24W (N=12)	Cohort A2: NA + IFN x 24W (N=13)	Cohort B1: IDR + NA + IFN x 12W (N=8)	Cohort B2: NA + IFN x 12W (N=10)	Study Total (N=43)
Any TEAE:	23 (53.5)	10 (83.3)	12 (92.3)	7 (87.5)	7 (70.0)	37 (86)
Grade 1	15 (34.9)	2 (16.7)	7 (53.8)	3 (37.5)	3 (30)	12 (27.9)
Grade 2	5 (11.6)	8 (66.7)	3 (23.1)	1 (12.5)	3 (30)	17 (39.5)
Grade 3	3 (7.0)[a]	0	2 (15.4)[b]	3 (37.5)[c]	1 (10.0)[d]	8 (18.6)
Grade 4	0	0	0	0	0	0
Related TEAEs: imdusiran	9 (20.9)	2 (16.7)	N/A	0	N/A	10 (23.3)
IFN	N/A	9 (75)	8 (61.5)	5 (62.5)	6 (60)	28 (65.1)
SAEs (both unrelated)[e]	0	1 (8.3)	0	0	1 (10)	2 (4.7)
Study discontinuation due to TEAEs	0	0	0	0	0	0
IFN dose modification	N/A	3 (25)	2 (15.3)	2 (25)	2 (20)	9 (20.9)

IDR: imdusiran; NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; W: weeks; TEAE: treatment emergent adverse event; SAE: serious adverse event
[a]2 Gr 3 ALT elevations (related), 1 Gr 3 rhabdomyolysis (unrelated); [b]2 Gr 3 neutrophil count decreased (related to IFN); [c]2 Gr 3 neutrophil count decreased & 1 Gr 3 ALT elevation (all related to IFN); [d]1 Gr 3 neutrophil count decreased (related to IFN)
[e]A1: ureteral stones requiring hospitalization; B2: nasal septal deviation and sinusitis requiring surgery

- The combination of imdusiran and IFN was well-tolerated with no related SAEs, no Grade 4 AEs and most Grade 3 AEs being lab abnormalities related to IFN

Figure 1: Mean Log_{10} HBsAg Change from Baseline by Cohort



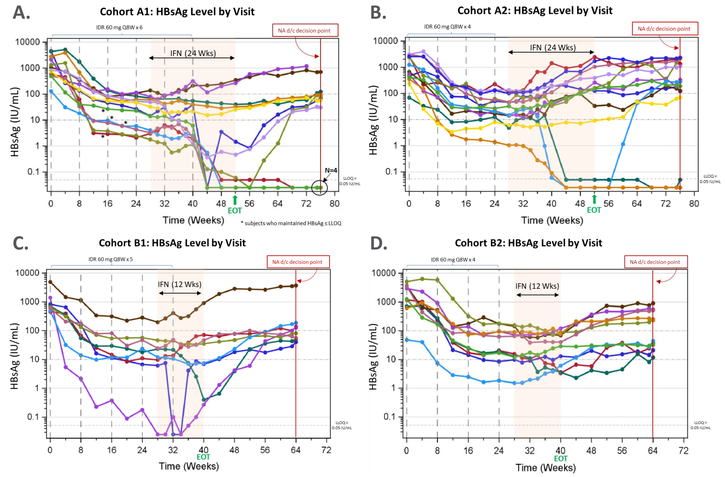
* p < 0.001 (by ANCOVA) for A1 vs all other cohorts at Week 52 and Week 76

Table 3: Number of Subjects with Undetectable HBsAg at Key Timepoints

Achieved HBsAg ≤ LLOQ (0.05 IU/mL)	Cohort A1: IDR x 6 + NA + IFN x 24W (N = 12)	Cohort A2: IDR x 4 + NA + IFN x 24W (N = 13)	Cohort B1: IDR x 5 + NA + IFN x 12W (N = 8)	Cohort B2: IDR x 4 + NA + IFN x 12W (N = 10)
Any time during treatment	6/12 (50%)	3/13 (23%)	2/8 (25%)	0/10
EOT	4/12 (33.3%)	3/13 (23%)	0/8	0/10
	7/25 (28%)		0/18	
Next Assay negative	4/4	2/3	N/A	N/A
24 weeks post-EOT (NA therapy only)	4/12 (33.3%)	2/13 (15.4%)	0/8	0/10
	6/25 (24%)		0/18	
Next Assay negative	2*/4 (*1 subject pending)	2/2	N/A	N/A
Discontinued NA therapy	9/12 (75%)	3/13 (23%)	4/8 (50%)	5/10 (50%)

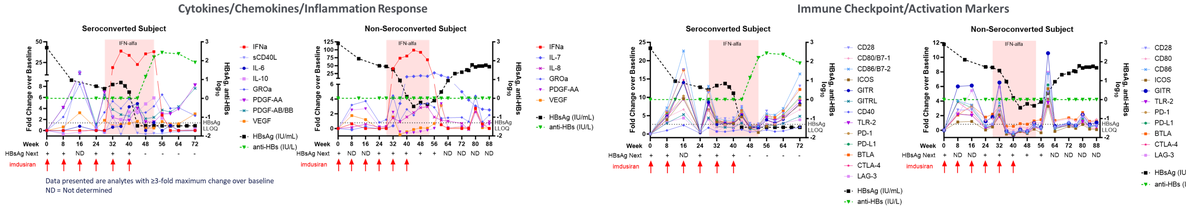
NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; W: weeks; EOT: end of treatment (Week 52 [A1/A2] or Week 40 [B1/B2]); Next Assay LLOD=0.005 IU/mL

Figure 2: Individual Subject HBsAg Levels by Cohort Over Time



- 24 vs 12 weeks of IFN and the continuation of imdusiran during IFN treatment led to greater HBsAg declines and more subjects reaching and maintaining HBsAg ≤LLOQ
- 6 of 7 subjects at EOT who were HBsAg ≤LLOQ were also Next Assay negative at EOT; all 6 of these subjects remained <LLOQ 24-weeks post-EOT
- All 6 subjects with sustained HBsAg ≤LLOQ during and after the treatment period seroconverted with high anti-HBs levels (range 43.8 to >1000 mIU/mL)
- All subjects with sustained HBsAg ≤LLOQ had baseline HBsAg levels <1000 IU/mL (range 68.6 – 576.3 IU/mL)

Figure 3: Preliminary Immune Biomarker Profiles of 2 Cohort A1 Subjects: 1 Seroconverted vs 1 Non-seroconverted Subject



Data presented are analytes with ≥3-fold maximum change over baseline
ND = Not determined

- 3 phases of immune biomarker elevation observed:
  - During imdusiran treatment lead-in
  - During IFN treatment
  - Post-IFN treatment, during anti-HBs antibody increases or HBsAg rebound
- Increases in immune biomarkers associated with immune activation/inflammation responses observed
  - Increased soluble immune checkpoint proteins such as PD-1 and PD-L1 suggests there may be benefit to targeting this axis to potentially prolong immune activation induced by imdusiran lead-in/IFN treatment
- Assessment of additional subjects and follow-up timepoints is ongoing

CONCLUSIONS

- More subjects in the 24-week IFN Cohorts (A1/A2) reached and maintained undetectable HBsAg than in the 12-week IFN cohorts (B1/B2); extending imdusiran dosing during IFN treatment also increased rates of HBsAg loss
  - 7/25 A1/A2 subjects (28%) had undetectable HBsAg at EOT (Week 52)
    - 4 from A1 (33.3%) and 3 from A2 (23%)
    - 6 of these 7 subjects were also negative via ultrasensitive Next Assay
  - 6 of these 7 subjects remained undetectable at 24 weeks post-EOT (Week 76)
    - 4 from A1 (33.3%), and 2 from A2 (15.4%)
    - 4 of 5 tested remain negative via ultrasensitive Next Assay (6th subject awaiting Next Assay analysis for 24 weeks post-EOT timepoint)
  - Subjects with sustained HBsAg loss seroconverted with high anti-HBs levels (43.8 to >1000 mIU/mL)
  - All 6 undetectable subjects (plus an additional 15 subjects from all 4 Cohorts, N=21 total) have discontinued NA treatment after the 24 weeks post-EOT visit
    - The first 2 of the 6 undetectable subjects have reached Week 12 off all therapy and have maintained both HBsAg and HBV DNA <LLOQ
    - 1 subject in Cohort B2 has achieved functional cure during the NA discontinuation period
    - As of the data cutoff date, 2 of the 21 subjects had restarted NA therapy due to HBV DNA >20,000 IU/mL without accompanying ALT increases
- Imdusiran 60 mg every 8 weeks in combination with IFN for 12 or 24 weeks was generally well-tolerated
  - Most common TEAEs related to imdusiran were transient ALT elevations in 3 subjects (7%) and injection site bruising in 2 subjects (4.7%)
  - IFN-related TEAEs were consistent with the known safety profile of IFN, most commonly decreased neutrophil counts, ALT elevations, pyrexia, and injection site erythema
  - 9 subjects required IFN dose modifications (reduced doses or dose interruption) due to laboratory abnormalities, did not appear to impact IFN efficacy
- Preliminary analysis of immune biomarkers suggests immune activation and inflammation responses are observed during imdusiran + NA treatment alone and after the addition of IFN
- This study remains ongoing; subjects will continue to be followed after NA discontinuation for evidence of functional cure

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ACKNOWLEDGEMENTS

Arbutus Biopharma thanks all participating subjects and their families, the Investigators and site staff, Novotech CRO and ProTrials Research, Q^2 Solutions, Maksym Chernyakhovskyy and Crystal Grant for data management assistance, and the imdusiran (AB-729) Research and Development Teams.

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