Imdusiran (AB-729) is safe and well tolerated after repeat dosing in chronic hepatitis B patients: An integrated safety analysis of Phase 1 and 2 imdusiran clinical trials

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BACKGROUND

- Current approved therapies for chronic hepatitis B (CHB) slow or prevent the development of hepatitis B virus (HBV)-related liver complications but do not typically lead to functional cure (FC).[1-4] Suppression of hepatitis B surface antigen (HBsAg) and other viral antigen production and induction of HBV-specific T-cell responses are likely required to achieve FC.[1]
- Imdusiran (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 production of all viral antigens.[5]
- Imdusiran has been studied in a Phase 1 and three Phase 2 studies combining imdusiran with immunomodulatory agents or a capsid assembly modulator (CAM). Individual studies have been presented separately previously and demonstrated the safety and tolerability of imdusiran in these trials; however, a combined analysis of the safety from all the trials had not been assessed previously.[6,7,8,9]
- The safety and tolerability of repeat (every 8 weeks) subcutaneous dosing of 60 mg or 90 mg of imdusiran when added to a background of nucleos(t)ide analogue (NA) therapy were evaluated in an integrated analysis of clinical trial results from over 150 CHB patients and is presented here.

MATERIALS AND METHODS

- Safety data including clinical and laboratory results were pooled and evaluated from subjects receiving repeat dose imdusiran (n=151, Fig.1) from the following trials:

Phase 1:

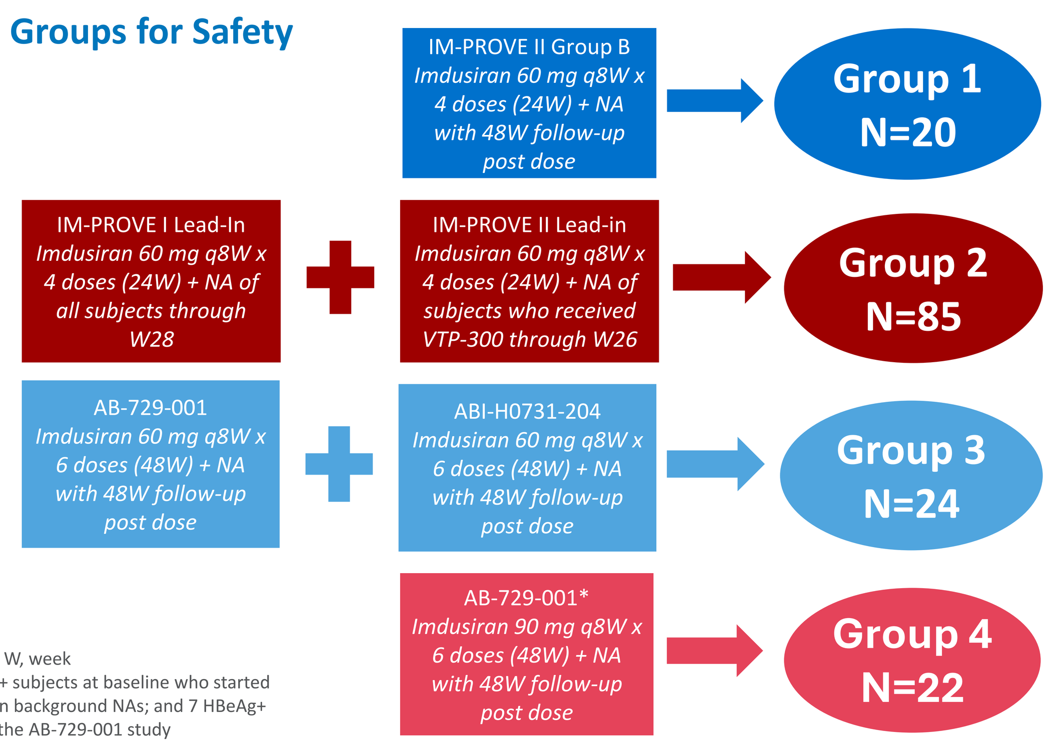
- AB-729-001; ACTRN12620000295943 – A Phase 1a/1b clinical trial evaluating the safety, tolerability, and PK/PD of single and multiple-ascending dose of imdusiran in healthy subjects and patients with CHB.

Phase 2:

- IM-PROVE I (AB-729-201); NCT04980482 – A randomized, open-label, multicenter Phase 2a study assessing the safety, tolerability and antiviral activity of 24 weeks of imdusiran 60 mg every 8 weeks followed by 12 or 24 weeks of pegylated interferon alfa-2a (IFN) with or without additional imdusiran doses in virally suppressed, HBeAg-negative CHB patients.
- IM-PROVE II (AB-729-202); ACTRN12622000317796 – A Phase 2a clinical trial evaluating the safety and immunogenicity of 24 weeks of imdusiran followed by VTP-300 (experimental immunotherapeutic) or placebo or VTP-300± low dose nivolumab in CHB patients.
- ABI-H0731-204; NCT04820686 – A Phase 2a study evaluating the safety and efficacy of vebicorvir (ABI-HO731, CAM) in combination with imdusiran in CHB patients.

- Patients were divided into 4 groups by treatment regimen and follow-up period for the safety analysis:
  - Group 1: IM-PROVE II subjects who received imdusiran 60 mg x 4 doses alone with safety data reported through 48 weeks after the last dose of imdusiran.
  - Group 2: All IM-PROVE I and remaining IM-PROVE II subjects (imdusiran 60 mg x 4 doses, considered as lead-in period) with safety data reported until the addition of immunotherapies in each of the studies (up to Week 28 and Week 26, respectively).
  - Group 3: AB-729-001 and ABI-H0731-204 subjects (imdusiran 60 mg x 6 doses in NA suppressed subjects) with safety data reported through 48 weeks after the last dose of imdusiran.
  - Group 4: AB-729-001 subjects from 3 unique cohorts who received imdusiran 90 mg x 6 doses with 48 weeks follow up safety data: HBV DNA+ subjects; HBeAg+/NA suppressed subjects; and HBeAg- and NA suppressed subjects.

Figure 1: Pooled Groups for Safety Analysis



NA, nucleos(t)ide analog; q, every; W, week
*Group 4 comprises of 7 HBV DNA+ subjects at baseline who started NAs on Day 1; 8 HBeAg- subjects on background NAs; and 7 HBeAg+ subjects on background NAs from the AB-729-001 study

RESULTS

Table 1: Demographics and Baseline Characteristics

Baseline Parameters	Group 1 Imdusiran 60 mg x 4 doses + NA N=20	Group 2 Imdusiran 60 mg x 4 doses + NA Lead-In N=85	Group 3 Imdusiran 60 mg x 6 doses + NA N=24	Group 4 Imdusiran 90 mg x 6 doses + NA N=22	Total N=151
Age, mean (SD), y	44.3 (8.33)	46.4 (7.82)	42.9 (7.65)	44.9 (9.29)	45.3 (8.11)
Males, n (%)	14 (70.0)	60 (70.6)	14 (58.3)	13 (59.1)	101 (66.9)
Race, n (%)					
Asian	19 (95.0)	72 (84.7)	15 (62.5)	18 (81.8)	124 (82.1)
White	1 (5.0)	8 (9.4)	7 (29.2)	2 (9.1)	18 (11.9)
Black or African Am	0	4 (4.7)	2 (8.3)	1 (4.5)	7 (4.6)
Genotype, n (%)*					
A	0	5 (5.9)	2 (8.3)	0	7 (4.6)
B	10 (50.0)	35 (41.2)	4 (16.7)	4 (18.2)	53 (35.1)
C	9 (45.0)	35 (41.2)	8 (33.3)	14 (63.6)	66 (43.7)
C/B	0	0	2 (8.3)	0	2 (1.3)
D	1 (5.0)	9 (10.6)	5 (20.8)	2 (9.1)	17 (11.3)
E	0	1 (1.2)	1 (4.2)	0	2 (1.3)
No data	0	0	2 (8.3)	2 (9.1)	4 (2.6)
HBeAg positive, n(%)	10 (50.0)	15 (17.6)	2 (8.3)	7 (31.8)	34 (22.5)
HBsAg (IU/mL)					
Mean (SD)	1135 (997.5)	1135 (998)	1105 (1093)	1296 (1468)	1148 (1092)
Median	870	720	3112	1825	1128
Range	100-3300	47.6-5109	198.6-18605	277.3-19017	47.6 - 19017
ALT, mean (SD), U/L	22.05 (11.12)	24.09 (10.59)	26.67 (16.50)	27.95 (11.83)	24.79 (11.96)
Baseline NA, n (%)					
ETV	10 (50.0)	33 (38.8)	4 (16.7)	6 (27.3)	53 (35.1)
TAF	4 (20.0)	26 (30.6)	2 (8.3)	2 (9.1)	34 (22.5)
TDF	6 (30.0)	26 (30.6)	18 (75.0)	7 (31.8) **	57 (37.7)

ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. *HBV Genotype was determined by Next Generation Sequencing (NGS). Samples which failed PCR amplification were genotyped using the IMMUNIS HBV Genotype EIA **7 subjects from Cohort G included in Group 4 were HBV DNA positive off NA therapy at baseline. TDF was initiated simultaneously with IDR in these 7 subjects.

- Demographics, such as age and race, and baseline mean HBsAg and ALT values were similar across all groups in the study (Table 1)
- The vast majority of CHB subjects across all studies were Asian, male and predominantly carried HBV Genotype C, followed by HBV Genotype B

Table 2: Summary of Treatment Emergent Adverse Events

Number (%) [Events] of Subjects with Any	Group 1 Imdusiran 60 mg x 4 doses + NA N=20	Group 2 Imdusiran 60 mg x 4 doses + NA Lead-In N=85	Group 3 Imdusiran 60 mg x 6 doses + NA N=24	Group 4 Imdusiran 90 mg x 6 doses + NA N=22	Total N=151
TEAE	17 (85.0) [68]	42 (49.4) [103]	17 (70.8) [83]	18 (81.8) [76]	94 (62.3) [330]
SAE	0	0	0	2 (9.1) [2]*	2 (1.3) [2]
TEAE related to imdusiran	2 (10.0) [6]	15 (17.6) [27]	9 (37.5) [26]	9 (40.9) [12]	35 (23.2) [71]
TEAE of Grade 3 or 4	0	3 (3.5) [3]	0	2 (9.1) [2]	5 (3.3) [5]
TEAE Grade 3 or 4 related to imdusiran	0	2 (2.4) [2]	0	0	2 (1.3) [2]
SAE related to imdusiran	0	0	0	0	0
TEAE leading to imdusiran discontinuation	0	0	1 (4.2) [1]**	0	1 (0.7) [1]
TEAE leading to study discontinuation	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0

NA, nucleos(t)ide analogue; SAE, serious adverse event; TEAE, treatment emergent adverse event; W, week; *1 SAE of a limb abscess and the other SAE of severe coronavirus infection. Both were unrelated to imdusiran; **1 subject in the ABI-H0731-204 study discontinued imdusiran early due to TEAE of Grade 2 ALT elevation meeting protocol stopping criteria

- There were no deaths, Grade 4 TEAEs or related SAEs reported in any of the subjects.
- There were a total of five Grade 3 TEAEs reported among the groups.
  - Only 2 subjects in Group 2 (imdusiran 60 mg x 4 doses + NA) had two Grade 3 ALT elevations related to imdusiran.
- Subjects who received 6 doses of imdusiran (60 or 90 mg) had similar rates of TEAEs as those who received 4 doses of imdusiran 60 mg.

Table 3: Summary of TEAEs Related to Imdusiran Occurring in 2 or More Subjects

Number (%) [Events] of Subjects with Any	Group 1 Imdusiran 60 mg x 4 doses + NA N=20	Group 2 Imdusiran 60 mg x 4 doses + NA Lead-In N=85	Group 3 Imdusiran 60 mg x 6 doses + NA N=24	Group 4 Imdusiran 90 mg x 6 doses + NA N=22	Total N=151
Injection site reactions:					
Bruising	1 (5.0) [2]	1 (1.2) [1]	0	1 (4.5) [1]	3 (2.0) [4]
Erythema	0	0	2 (8.3) [2]	1 (4.5) [1]	3 (2.0) [3]
Pain	0	3 (3.5) [7]	4 (16.7) [12]	5 (22.7) [5]	12 (7.9) [24]
Swelling	1 (5.0) [1]	0	1 (4.2) [1]	0	2 (1.3) [2]
ALT increased	1 (5.0) [2]	5 (5.9) [6]	2 (8.3) [3]	1 (4.5) [1]	9 (6.0) [12]
Dizziness	0	1 (1.2) [1]	1 (4.2) [1]	0	2 (1.3) [2]
Erythema	0	3 (3.5) [3]	0	2 (9.1) [2]	2 (1.3) [2]
Fatigue	0	1 (1.2) [1]	2 (8.3) [2]	0	3 (2.0) [3]
Headache	0	1 (1.2) [2]	1 (4.2) [1]	0	2 (1.3) [3]
Nausea	0	1 (1.2) [1]	0	1 (4.5) [1]	2 (1.3) [2]
Pruritus	0	1 (1.2) [2]	1 (4.2) [1]	0	2 (1.3) [2]

ALT, alanine transaminase; NA, nucles(t)ide analogue ; W, week

- The most frequently reported TEAE in CHB patients who received imdusiran was injection site reactions, followed by ALT increases
  - All injection site reactions were Grade 1, with the exception of one subject with a Grade 2 injection site pain TEAE in Group 2 (imdusiran 60 mg x 4 doses + NA)
- All TEAEs were Grades 1 or 2, except for two TEAEs of ALT increases in Group 2 which were Grade 3 and resolved.

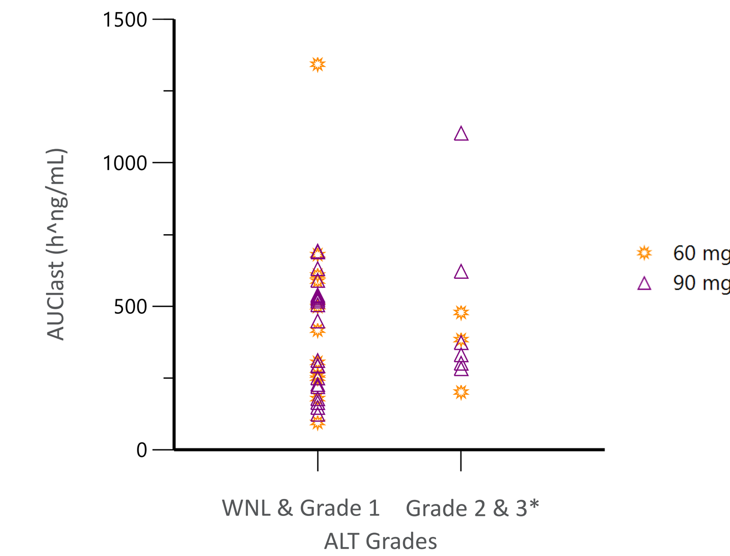
Table 4: Treatment-Emergent Laboratory Abnormalities Observed in ≥10% of Subjects

Number (%) Subjects with	Group 1 Imdusiran 60 mg x 4 doses + NA N=20	Group 2 Imdusiran 60 mg x 4 doses + NA Lead-In N=85	Group 3 Imdusiran 60 mg x 6 doses 48W+NA N=24	Group 4 Imdusiran 90 mg x 6 doses 48W+NA N=22	Total N=151
Postbaseline Value	19 (95.0)	64 (75.3)	23 (95.8)	20 (90.9)	126 (83.4)
Grade 1	6 (30.0)	42 (49.4)	5 (20.9)	11 (50.0)	64 (42.4)
Grade 2	9 (45.0)	17 (20.0)	14 (58.3)	6 (27.3)	46 (30.5)
Grade 3	3 (15.0)	4 (4.7)	3 (12.5)	3 (13.6)	13 (8.6)
Grade 4	1 (5.0)	1 (1.2)	1 (4.2)	0	3 (2.0)
ALT (U/L)	7 (35.0)	38 (44.7)	11 (45.8)	16 (72.7)	72 (47.7)
Grade 1	3 (15.0)	30 (35.3)	8 (33.3)	10 (45.5)	51 (33.8)
Grade 2	2 (10.0)	6 (7.1)	1 (4.2)	6 (27.3)	15 (9.9)
Grade 3	2 (10.0)	2 (2.4)	2 (8.3)	0	6 (4.0)
AST (U/L)	5 (25.0)	20 (23.5)	7 (29.2)	10 (45.5)	42 (27.8)
Grade 1	2 (10.0)	16 (18.8)	5 (20.8)	9 (40.9)	32 (21.2)
Grade 2	1 (5.0)	3 (3.5)	2 (8.3)	1 (4.5)	7 (4.6)
Grade 3	2 (10.0)	1 (1.2)	0	0	3 (2.0)
CK (IU/L)	4 (20.0)	7 (8.2)	2 (8.3)	3 (13.5)	16 (10.6)
Grade 1	0	4 (4.7)	0	2 (9.1)	6 (4.0)
Grade 2	3 (15.0)	1 (1.2)	1 (4.2)	0	5 93.3)
Grade 3	0	1 (1.2)	0	1 (4.5)	2 (1.3)
Grade 4	1(5.0)	1 (1.2)	1 (4.2)	0	3 (2.0)
Glucose (mmol/L)	5 (25.0)	8 (9.4)	9 (37.5)	3 (13.6)	25 (16.6)
Grade 1	2 (10.0)	5 (5.9)	4 (16.7)	2 (9.1)	13 (8.6)
Grade 2	3 (15.0)	3 (3.5)	5 (20.8)	1 (4.5)	12 (7.9)
PTT (sec)	10 (50.0)	14 (16.5)	0	0	24 (15.9)
Grade 1	7 (35.0)	10 (11.8)	0	0	17 (11.3)
Grade 2	2 (10.0)	4 (4.7)	0	0	6 (4.0)
Grade 3	1 (5.0)	0	0	0	1 (0.7)

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; NA, nucles(t)ide analogue; PTT, partial thromboplastin time; W, week

- The most common lab abnormalities in subjects were elevations in ALT, followed by AST elevations.
  - There were a greater proportion of ALT abnormalities in Group 4 (IDR 90 mg x 6 doses) compared to the other groups, but these elevations were clinically mild to moderate (Grades 1-2).
    - The 6 Grade 2 ALT elevations were ≥ 2.5 ULN, but not ≥ 5xULN. These ALT elevations corresponded to HBsAg declines occurring in these subjects at the same time.
    - The number of Grade 2 ALT elevations did not result in more TEAEs reported in Group 4 compared to the other groups.
- The only Grade 4 lab abnormalities were 3 creatine kinase elevations in Groups 1-3. None were related to imdusiran and all 3 were likely related to strenuous exercise.

Figure 2: Imdusiran AUC vs. ALT Elevations



ALT, alanine transaminase; AUC , area under the curve; WNL, within normal limits *6 Grade 3 abnormalities in 60 mg x 4-6 doses with only 2 related to imdusiran; all were transient and resolved; no reported Grade 3 ALT abnormalities in 90 mg x 6 doses; no Grade 4 ALT elevations in either dose group

- There was no apparent dose exposure relationship with the incidence of ALT abnormalities (Figure 2).
- Group 4 (90 mg x 6 doses) had a greater incidence of ALT/AST lab abnormalities; however, Group 4 included 7 subjects who were HBV DNA+ at baseline as well as 7 subjects who were HBeAg+ at baseline.
  - Only 1 ALT elevation among this group was considered a TEAE

CONCLUSIONS

- 4 or 6 doses of imdusiran at 60 mg or 90 mg were well tolerated.
- No deaths, Grade 4 TEAEs, or IDR-related SAEs occurred in any of the patients included in this analysis.
- The most common imdusiran related TEAEs were injection site reactions and ALT increase, with the majority being Grade 1 or 2.
- The most common laboratory abnormality was Grade 1 or 2 ALT or AST elevations. Most abnormalities were not considered TEAEs or clinically significant and returned to baseline during ongoing imdusiran dosing and without other intervention.
- The safety profiles of imdusiran 60 mg versus imdusiran 90 mg for 4 or 6 doses were similar, with no TEAE or laboratory trends noted with more doses or higher dose levels of imdusiran.

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