IM-PROVE I: HBV genotype responsiveness to pegylated interferon alfa-2a may be enhanced with imdusiran combination treatment

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Arbutus BIOPHARMA Curing Chronic Hepatitis B

BACKGROUND

Functional cure of chronic hepatitis B (CHB) requires suppression of HBV replication, antigens and induction of anti-HBV immune responses. Imdusiran is an *N*-Acetylgalactosamine–conjugated, pan-genotypic small interfering RNA that blocks all HBV RNA, resulting in suppression of viral replication and all antigens.

IM-PROVE I is a Phase 2a study assessing combination treatment of imdusiran with pegylated interferon alfa-2a (IFN) in HBeAg-negative nucleots(t)ide analog (NA) treated CHB subjects.

HBV genotypes are known to influence response to IFN, with the greatest HBsAg declines in genotype A and the lowest response for genotype C in HBeAg-negative patients[1]. The association of genotypes with HBsAg response during IFN treatment with imdusiran dosing and end-of-study clinical outcomes for subjects in IM-PROVE I is presented.

Table 1: Subjects Achieving Functional Cure in IM-PROVE I

Functional Cure	Cohort A1: Imdusiran x 6 doses + NA + IFN x 24W (N = 12)	Cohort A2: Imdusiran x 4 doses + NA + IFN x 24W (N = 13)	Cohort B1: Imdusiran x 5 doses + NA + IFN x 12W (N = 8)	Cohort B2: Imdusiran x 4 doses + NA + IFN x 12W (N = 10)
All Subjects	3/12 (25%)	2/13 (15%)	0/8	1/10 (10%)
Those with HBsAg <1000 IU/mL at Baseline	3/6 (50%)	2/7 (29%)	0/6	0/4

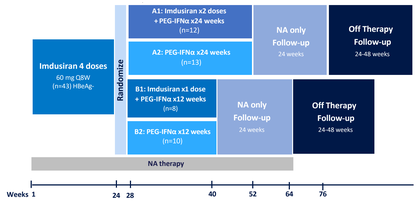
Functional cure defined as sustained HBsAg loss and HBV DNA less than lower limit of quantification (LLOQ) 24 weeks off-treatment, with or without hepatitis B surface antibodies[2].

OBJECTIVES

- Assess association of HBV genotype with HBsAg response during IFN treatment with imdusiran dosing
- Determine association of HBV genotypes with clinical outcomes for IM-PROVE I study patients

MATERIALS AND METHODS

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



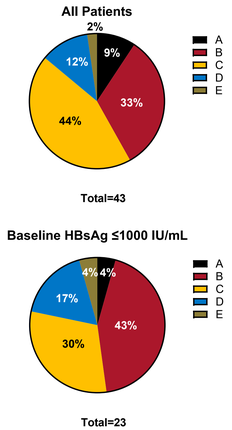
- IM-PROVE I enrolled 43 non-cirrhotic, HBeAg-negative, virally suppressed CHB subjects on stable NA therapy for at least 12 months prior to Day 1
- All subjects received 24 weeks (4 doses) of imdusiran 60 mg every 8 weeks (Q8W) and were randomized at Week 24 into one of 4 groups (stratified by HBsAg level ≤100 or >100 IU/mL at Week 24)
- Patients in Cohort A1 received 2 additional doses of imdusiran and those in Cohort B1 received 1 additional dose of imdusiran after randomization
- After completion of the IFN treatment period, patients were followed for an additional 24 weeks on NA therapy alone, then assessed for NA discontinuation via protocol-defined criteria:
  - ALT <2x ULN and undetectable HBV DNA and HBsAg <100 IU/mL at 2 consecutive visits at least 24 weeks after completion of IFN treatment
- Mean (SD) age across patients was 45.3 (6.4) and 28% were female. Baseline characteristics were presented previously[3,4]
- Baseline samples were collected from 43 subjects and HBV genotype was determined by deep sequencing[5] and alignment to HBV genotype reference sequences
- Samples which were unable to be sequenced were serotyped using the IMMUNIS®HBV Genotype EIA assay

RESULTS

1. HBV Genotypes in IM-PROVE I

OVERALL STUDY HBV Genotypes % (n)	Cohort A1 (N = 12)	Cohort A2 (N = 13)	Cohort B1 (N = 8)	Cohort B2 (N = 10)	Total (N=43)
A	0	15% (2)	0	20% (2)	9% (4)
B	33% (4)	38% (5)	37.5% (3)	20% (2)	33% (14)
C	50% (6)	31% (4)	50% (4)	50% (5)	44% (19)
D	17% (2)	8% (1)	12.5% (1)	10% (1)	12% (5)
E	0	8% (1)	0	0	2% (1)

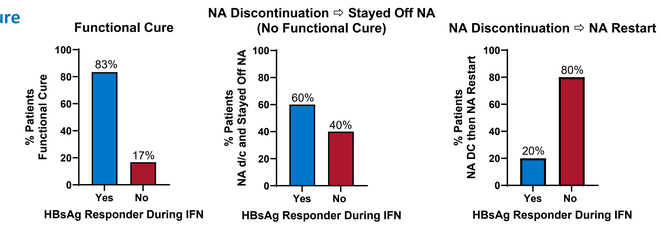
BASELINE HBsAg ≤1000 IU/mL HBV Genotypes % (n)	Cohort A1 (N = 6)	Cohort A2 (N = 7)	Cohort B1 (N = 6)	Cohort B2 (N = 4)	Total (N=23)
A	0	14% (1)	0	0	4% (1)
B	33% (2)	43% (3)	50% (3)	50% (2)	43% (10)
C	33% (2)	14% (1)	33% (2)	50% (2)	30% (7)
D	33% (2)	14% (1)	17% (1)	0	17% (4)
E	0	14% (1)	0	0	4% (1)



- 77% of patients enrolled in IM-PROVE I were HBV genotype B or C, as expected given predominantly Asian enrollment
- Similarly, 73% of patients with baseline HBsAg ≤1000 IU/mL were HBV genotypes B and C

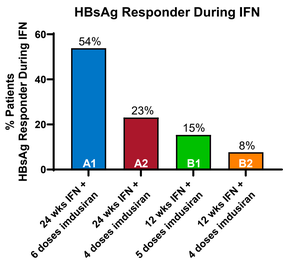
2. HBsAg Response During IFN Is Associated with Functional Cure

- HBsAg response was defined as ≥0.5 $\log_{10}$ reduction from the value observed after 4 initial doses of imdusiran (pre-randomization; Week 28) through to end of IFN treatment. Notably, during IFN treatment, HBsAg response has been associated with sustained virological response/HBsAg loss in CHB patients undergoing IFN therapy[6]
- Of the patients who achieved functional cure in IM-PROVE I, 83% (5/6) were HBsAg responders during IFN treatment
- 60% of patients (6/10) who met NA discontinuation criteria and remained off NA therapy (no functional cure) through to end of study were also HBsAg responders during IFN treatment
- Conversely, 80% (4/5) of the patients who eventually restarted NA therapy had not shown a HBsAg response during the IFN treatment period

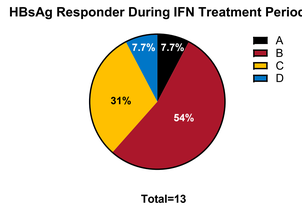


3. Majority of HBsAg Responders During IFN Were Treated with 24 Weeks IFN + 6 Doses Imdusiran

- The majority of patients who were HBsAg responders during IFN were from Cohort A1 (24 weeks IFN + 6 doses imdusiran, in total)
- After randomization, additional doses of imdusiran were associated with greater numbers of patients achieving HBsAg response during IFN treatment (Cohort A1 vs A2, Cohort B1 vs B2)

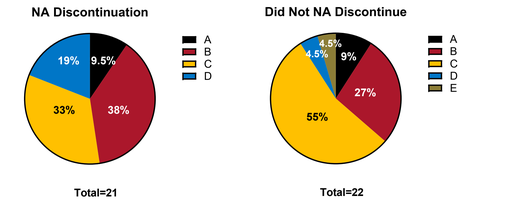


4. HBsAg Responders Spanned HBV Genotypes A to D

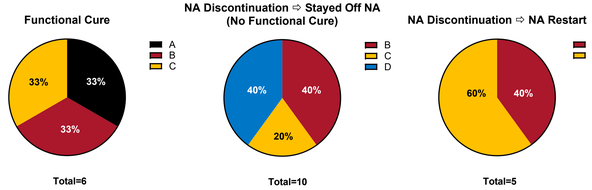


- Patients who were HBsAg responders spanned HBV genotypes A to D
- 54% of HBsAg responders during IFN treatment were HBV genotype B
- Interestingly, 31% were HBV genotype C: HBeAg-negative patients with this genotype were previously described as having the lowest response to IFN therapy[1]

5. HBV Genotypes and Clinical Outcomes



- Patients who met or did not meet NA discontinuation criteria spanned multiple HBV genotypes



- Patients who achieved functional cure were distributed across HBV genotypes A, B, and C (2/6 each)
- Patients who met NA discontinuation criteria and remained off NA therapy through to end of study (no functional cure) were comprised of HBV genotypes B, C and D
- Patients who were HBV genotype C made up the majority of those who had to restart NA therapy; this was also the most predominant genotype in the overall study

CONCLUSIONS

- HBsAg response during IFN treatment was associated with favorable clinical outcomes such as achieving functional cure or remaining off NA therapy in IM-PROVE I
- Patients who were HBsAg responders during IFN treatment spanned HBV genotypes A to D
- Patients who achieved functional cure were evenly distributed across HBV genotypes A, B and C
- The achievement of HBsAg responsiveness and favorable clinical outcomes across a range of HBV genotypes after IFN treatment suggests that imdusiran may enhance responsiveness to IFN in HBV genotypes that were previously described as poor responders to this immunomodulatory treatment

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