IM-PROVE I: Rapid loss followed by transient increases in HBV RNA in chronic hepatitis B subjects during treatment with imdusiran and pegylated interferon alfa-2a is associated with HBsAg seroclearance

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BACKGROUND

Imdusiran (IDR) is an *N*-Acetylgalactosamine (GalNAc)-conjugated siRNA that targets all HBV RNA transcripts including HBx, resulting in reduction of all viral antigens including HBsAg and stimulation of anti-HBV immunity. Pegylated interferon alfa-2a (IFN) is an approved immunomodulator with limited efficacy against HBV. In a completed Phase 2a study assessing IDR lead-in treatment (24 weeks) followed by 12 or 24 weeks of IFN ± additional IDR doses in HBeAg-negative CHB subjects virally suppressed on nucleos(t)ide analog (NA) therapy (IM-PROVE I), 6 subjects achieved functional cure (FC, defined as HBsAg and HBV DNA <LLOQ for 24 weeks off all treatment)[1].

Exploratory HBV and immunological biomarker profiling of these functional cure subjects is presented here. Subjects with sustained HBV DNA after NA discontinuation and HBsAg maintained ≤100 IU/mL are included for comparison.

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

Achieved HBsAg ≤ LLOQ (0.05 IU/mL)	Cohort A1: IDR x 6 doses + NA + IFN x 24W (N = 12)	Cohort A2: IDR x 4 doses + NA + IFN x 24W (N = 13)	Cohort B1: IDR x 5 doses + NA + IFN x 12W (N = 8)	Cohort B2: IDR x 4 doses + NA + IFN x 12W (N = 10)
EOT	4/12 (33%)	3/13 (23%)	0/8	0/10
Baseline HBsAg <1000 IU/mL	4/6 (67%)	2/7 (29%)	0/6	0/4
Abbott Next Assay negative	4/4	2/3	N/A	N/A
24 weeks post-EOT (NA therapy only)	4/12 (33%)	2/13 (15%)	0/8	0/10
Baseline HBsAg <1000 IU/mL	4/6 (67%)	2/7 (29%)	N/A	N/A
Abbott Next Assay negative	3/4	2/2	N/A	N/A
Functional Cure (FC)	3/12 (25%)	2/13 (15%)	0/8	1/10
FC Baseline HBsAg <1000 IU/mL	3/6 (50%)	2/7 (29%)	N/A	0/4
Abbott Next Assay negative	3/3	2/2	N/A	1/1
EOS				
FC Baseline HBsAg <1000 IU/mL	3/6 (50%)	2/7 (29%)	N/A	0/4
Abbott Next Assay negative	2/3	1/2	N/A	1/1

See **Poster THU-260 for a review of functional cure subjects' baseline characteristics.** N/A = Not applicable. Abbott HBsAg Next Assay LLOD = 0.005 IU/mL. Functional cure defined as sustained HBsAg <0.05 IU/mL and HBV DNA less than lower limit of quantification (LLOQ) 24 weeks off-NA treatment, with or without hepatitis B surface antibodies[2].

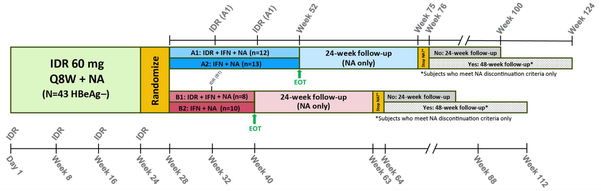
OBJECTIVES

- Profile exploratory HBV biomarkers (HBV RNA, HBcrAg, HBsAg isoforms, HBsAg Next Assay) in subjects who achieved functional cure in IM-PROVE I
- Compare HBV biomarker profiles with immunological exploratory endpoints

MATERIALS AND METHODS

- Longitudinal serum/plasma samples were assessed for HBV markers:
  - 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[3]
  - HBV RNA was assessed via Abbott v2.0 RUO assay; LLOQ = 0.49 log10 U/mL or 3.0 U/mL
  - Anti-HBs was assessed with Elecsys® Anti-HBs II (Roche); LLOQ = 2 or 3.5 IU/L
  - HBcrAg was assessed with Fujirebio Lumipulse G; LLOQ = 1.0 kU/mL
  - HBsAg isoforms were assessed via Abbott RUO assays[4]
  - HBV-specific T cell activation and proliferation was assessed by IFN-γ/IL-2/TNF-α fluorospot (Mabtech) and a ^{3}H-thymidine incorporation assay[5]
  - Immune biomarkers were assessed using Luminex multiplex assays

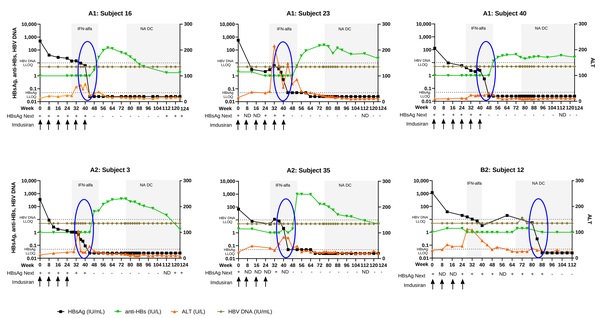
Study Design for Phase 2a Study IM-PROVE I



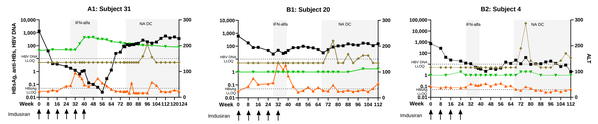
RESULTS

1. Functional Cure Subjects Experience Similar Pattern of HBsAg Loss and Seroconversion Following Imdusiran + 24-Week pegIFN-α2a Treatment

Functional Cure Subjects



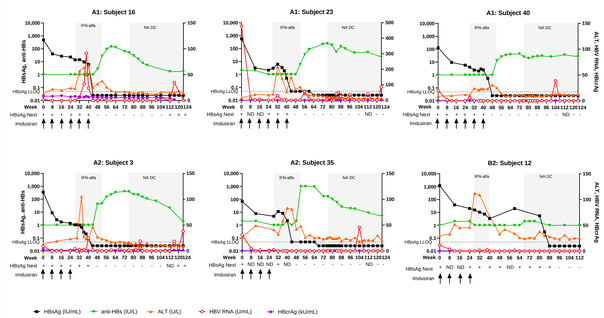
Subjects with Sustained HBV DNA Suppression with Transient HBV DNA Blips



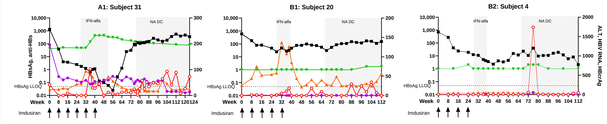
- After reaching nadir of HBsAg reduction during IDR lead-in, a further decline in HBsAg is observed after ~12 weeks of IFN dosing in the 5 FC subjects who received 24 weeks of IFN treatment
- One subject who achieved functional cure in the 12-week IFN treatment cohort (B2) did not show HBsAg decline during IFN treatment, but did during NA discontinuation, suggesting different mechanism for FC
- Declines were preceded by transient ALT elevations (see also **Poster THU-260**) in FC subjects and Subject 31 who also had further HBsAg decline during IFN treatment
- Subjects 16 and 3 are reactive by HBsAg Next Assay on Weeks 112 through 124 but remain negative by conventional HBsAg quantitative assay
- All FC subjects are currently being followed in rollover study AB-729-204 to assess durability of functional cure

2. HBsAg Seroclearance Associated with Transient HBV RNA Elevations

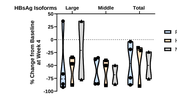
Functional Cure Subjects



Subjects with Sustained HBV DNA Suppression with Transient HBV DNA Blips

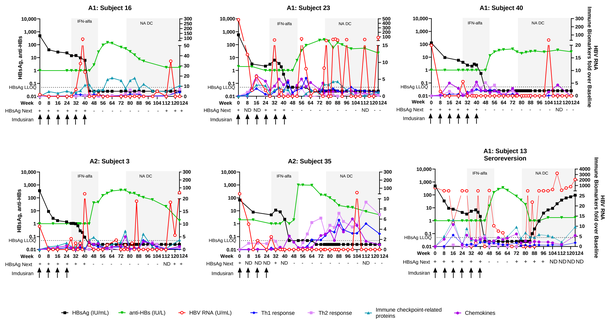


- HBV RNA declines during IDR lead-in as anticipated based on IDR's RNAi mechanism of action
- However, transient spikes in HBV RNA were observed during the nadir of HBsAg reduction in the IDR lead-in period, and also occurred during IFN treatment
- Increase in HBV RNA did not coincide with increase in HBcrAg
- HBV RNA elevations during IFN treatment coincided with the additional HBsAg decline observed during this period
- At Week 4, reductions in Large, Middle and Total HBsAg isoforms were similar across subjects
- By Week 124, reductions ranged from 72 – 100% for Large, 69 – 100% for Middle isoforms



3. Immune Biomarker Elevations Coincided or Followed HBV RNA Elevations

Functional Cure Subjects



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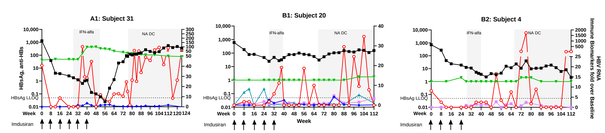
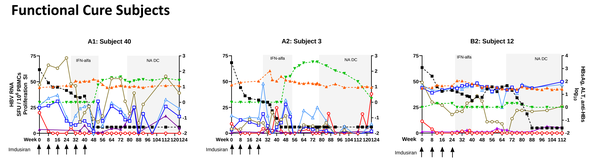


Immune biomarkers were grouped in categories and data presented are means of grouped analytes. Th1 = IFN-g, IL-2, IL-10, IL-12(p70), IP-10, CD40L, IL-12(p40), TNFa, IL-1b. Th2 = IL-4, IL-5, IL-6, IL-13. Immune checkpoint related proteins = sBTLA, sCD28, sGITR, sCTLA-4, sCD86, sPD-1, sPD-L1. Chemokines = GROa, PDGF-AA, PDGF-AB/BB, IL-8.

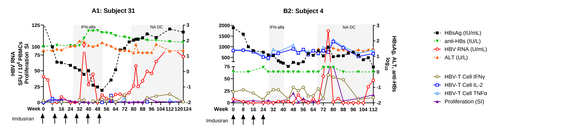
- Increases in Th1, Th2, chemokines and soluble immune checkpoint proteins preceded or occurred concomitantly with transient HBV RNA elevations
- Generally greater breadth of immune biomarker elevations observed in subjects who lost HBsAg compared to subjects who have sustained HBV DNA suppression but no HBsAg loss

4. HBV-Specific T Cell Responses Increase Prior to and During HBV RNA Elevation During IFN Treatment and Before Seroconversion

Functional Cure Subjects

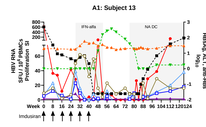


Subjects with Sustained HBV DNA Suppression with Transient HBV DNA Blips



- Preliminary assessment of 3/6 FC subjects thus far suggests that in some subjects, HBV-specific T cell responses are elevated at:
  - Nadir of HBsAg decline at the end of the imdusiran lead-in period
  - Beginning of seroconversion period

Seroreversion Subject



- Subject who seroreverted at Week 86 did not have elevated HBV-specific T cell responses at the beginning of their seroconversion period
- HBsAg becomes quantifiable as anti-HBs levels fall, suggesting masking of HBsAg due to immune complexes

CONCLUSIONS

- Subjects who achieve functional cure after treatment with imdusiran + 24 weeks of IFN share similar pattern of HBsAg loss occurring after 12 weeks of IFN treatment, followed by seroconversion
  - This pattern is not apparent in subjects who did not achieve FC but have sustained HBV DNA suppression after NA discontinuation
- HBsAg seroclearance during IFN treatment was associated with transient HBV RNA elevations that did not coincide with HBcrAg increases; HBsAg isoform reductions were also similar across tested subjects
- Soluble immune biomarkers were elevated during or following these HBV RNA elevations
- Preliminary assessment suggests that HBV-specific T cell activity is elevated at the nadir of HBsAg decline during imdusiran lead-in and prior to seroconversion. Further assessment of additional subjects is ongoing.
- Potential masking of HBsAg was observed in one seroreversion subject
- Taken together, these profiles across exploratory viral and immunological markers suggest an interplay of HBV RNA release and induction of HBV immune responses that was associated with HBsAg loss in these functional cure subjects

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