Soluble Immune Biomarker Profiling of Chronic Hepatitis B Subjects Treated with Imdusiran in Combination with Pegylated Interferon Alfa Reveals Phases of Immune Activation

Christine L Espiritu[1], Sharie C Ganchua[1], Timothy Eley[1], Kevin Gray[1], Man-Fung Yuen[2], Jeong Heo[3], Ronald G Nahass[4], Grace Lai-Hung Wong[5], Tatiana Burda[6], Kalyan Ram Bhamidimarri[7], Tsung-Hui Hu[8], Tuan T Nguyen[9], Young-Suk Lim[10], Chi-Yi Chen[11], Stuart C Gordon[12], Jacinta Holmes[13], Wan-Long Chuang[14], Anita Kohli[15], Naim Alkhouri[15], Angela M Lam[1], Michael J Sofia[1], Karen D Sims[1], Emily P Thi[1]

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

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BACKGROUND

Imdusiran (IDR) is a *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 an ongoing Phase 2a study[1] 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), **soluble immune biomarkers were profiled and association with functional cure was assessed**.

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)
Any time during treatment	6/12 (50%)	3/13 (23%)	2/8 (25%)	0/10
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

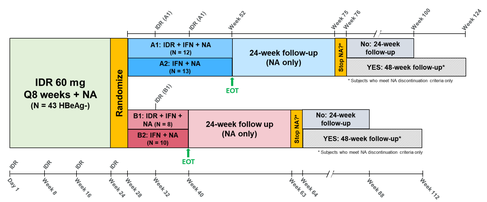
See Late Breaker Poster # 5036[2]. N/A = Not applicable. Abbott HBsAg Next Assay LLOD = 0.005 IU/mL[3]
Functional cure defined as sustained HBsAg loss and HBV DNA less than lower limit of quantification (LLOQ) 24 weeks off-treatment, with or without hepatitis B surface antibodies[4].

OBJECTIVES

- Characterize soluble immune biomarker profiles in subjects achieving functional cure in IM-PROVE I
- Compare immune biomarker profiles across 12- and 24-week IFN treatment regimens
- Compare immune biomarker profiles within 24-week IFN treatment regimens with or without additional IDR doses

MATERIALS AND METHODS

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

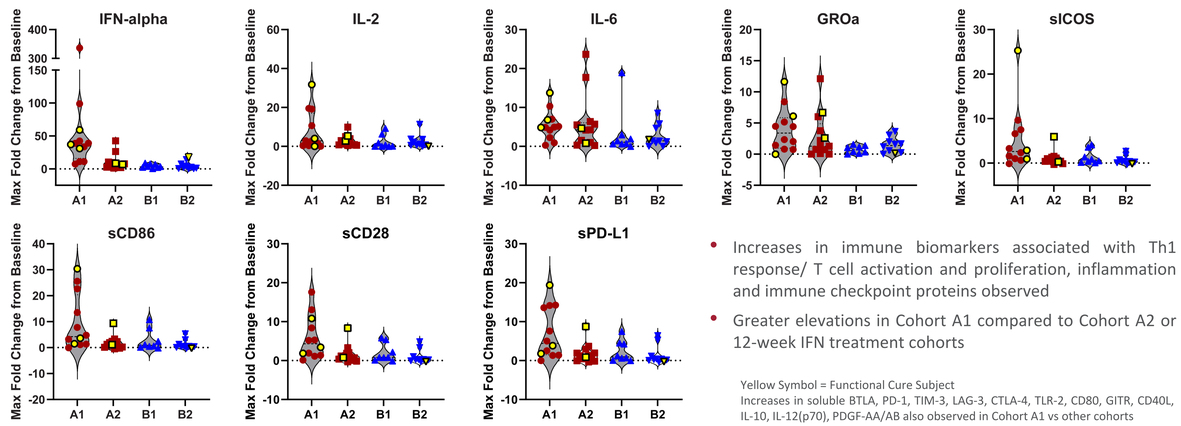


- IM-PROVE I enrolled 43 non-cirrhotic, HBeAg-negative, virally suppressed CHB subjects on stable NA therapy for at least 12 months prior to Day 1
- All subjects received 24 weeks (4 doses) of imdusiran 60 mg every 8 weeks (Q8W) and were randomized at Week 24 into one of 4 groups (stratified by HBsAg level ≤100 or >100 IU/mL at Week 24)
- 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 protocol-defined criteria (see Late Breaker Poster 5036[2])

- Longitudinal plasma samples were collected from 43 subjects during the 24-week IDR lead-in, IFN treatment and follow-up periods
- Soluble immune biomarkers were assessed using Luminex multiplex panels (58 analytes)

RESULTS

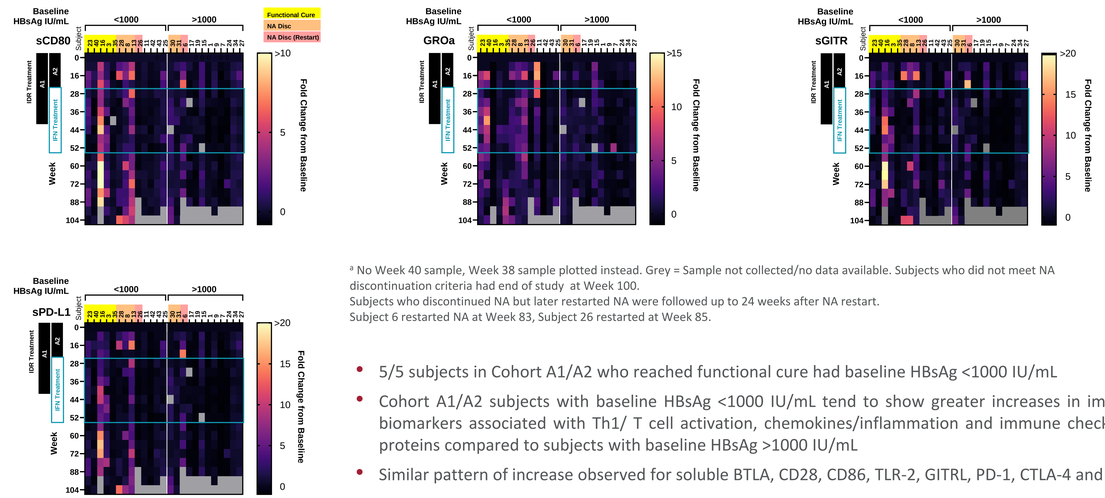
Greater Elevations in Immune Biomarkers Observed with IDR Lead-in + 24-Week IFN/Concurrent IDR Treatment (Cohort A1)



- Increases in immune biomarkers associated with Th1 response/ T cell activation and proliferation, inflammation and immune checkpoint proteins observed
- Greater elevations in Cohort A1 compared to Cohort A2 or 12-week IFN treatment cohorts

Yellow Symbol = Functional Cure Subject
Increases in soluble BTLA, PD-1, TIM-3, LAG-3, CTLA-4, TLR-2, CD80, GITR, CD40L, IL-10, IL-12(p70), PDGF-AA/AB also observed in Cohort A1 vs other cohorts

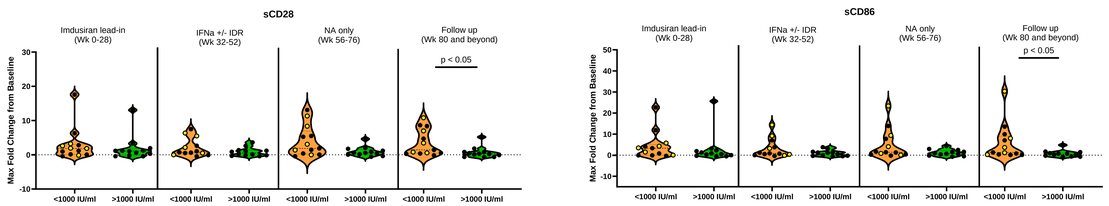
Elevations in Immune Biomarkers Appear During IDR Lead-in and Continue Throughout 24 Week IFN ± IDR Treatment in Functional Cure Subjects



[a] No Week 40 sample, Week 38 sample plotted instead. Grey = Sample not collected/no data available. Subjects who did not meet NA discontinuation criteria had end of study at Week 100.
Subjects who discontinued NA but later restarted NA were followed up to 24 weeks after NA restart.
Subject 6 restarted NA at Week 83, Subject 26 restarted at Week 85.

- 5/5 subjects in Cohort A1/A2 who reached functional cure had baseline HBsAg <1000 IU/mL
- Cohort A1/A2 subjects with baseline HBsAg <1000 IU/mL tend to show greater increases in immune biomarkers associated with Th1/ T cell activation, chemokines/inflammation and immune checkpoint proteins compared to subjects with baseline HBsAg >1000 IU/mL
- Similar pattern of increase observed for soluble BTLA, CD28, CD86, TLR-2, GITRL, PD-1, CTLA-4 and ICOS

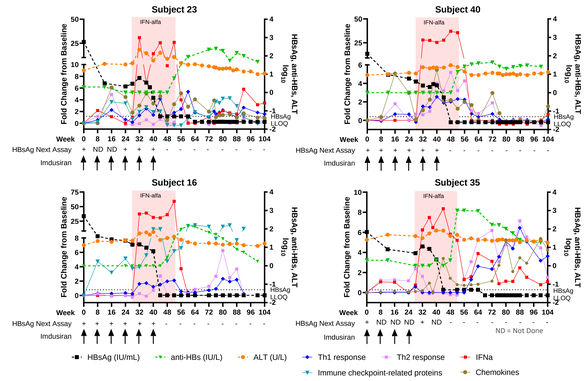
Subjects with Baseline HBsAg <1000 IU/mL Show High Levels of Soluble T Cell Activation Markers After Completion of IDR Lead-in + 24 Weeks IFN ± IDR Treatment



- Greatest increases occur after end of IFN ± IDR treatment (NA only) and during follow-up

P < 0.05 by Mann-Whitney test
Yellow Symbol = Functional Cure Subject

Phases of Immune Activation Observed in Functional Cure Subjects



- In Cohort A1/A2 Functional Cure subjects, elevations in Th1 cytokines, chemokines/inflammation and immune checkpoint proteins observed during IDR lead-in and IFN treatment
- Th2 cytokines increased during IDR lead-in and concurrent IFN treatment and were associated with HBsAg seroconversion for 4/5 of these subjects

- Subject 3 in Cohort A2 who reached functional cure showed elevations in Th2 cytokines late during follow-up period

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.

CONCLUSIONS

- Subjects treated with IDR lead-in followed by IDR + IFN for an additional 24 weeks (Cohort A1) have higher elevations of immune biomarkers compared to subjects where IDR was only administered during lead-in (Cohort A2) or subjects in 12-week IFN treatment regimens
- Phases of immune biomarker signatures are observed during IDR lead-in, IFN treatment and HBsAg seroconversion in this set of functional cure subjects
- Subjects with HBsAg <1000 IU/mL at baseline show greater increases in immune biomarkers during IDR lead-in, IFN treatment and follow-up
- These data suggest that subjects with baseline HBsAg <1000 IU/mL respond well to immune activation induced by IDR + IFN treatment and support further development of this combination treatment in this population

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CONTACT

Emily Thi, ethi@arbutusbio.com
Sr. Director
Immunology and Biomarkers Research

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