Imdusiran: Sustained HBsAg Suppression and Host Immune Control

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CSO

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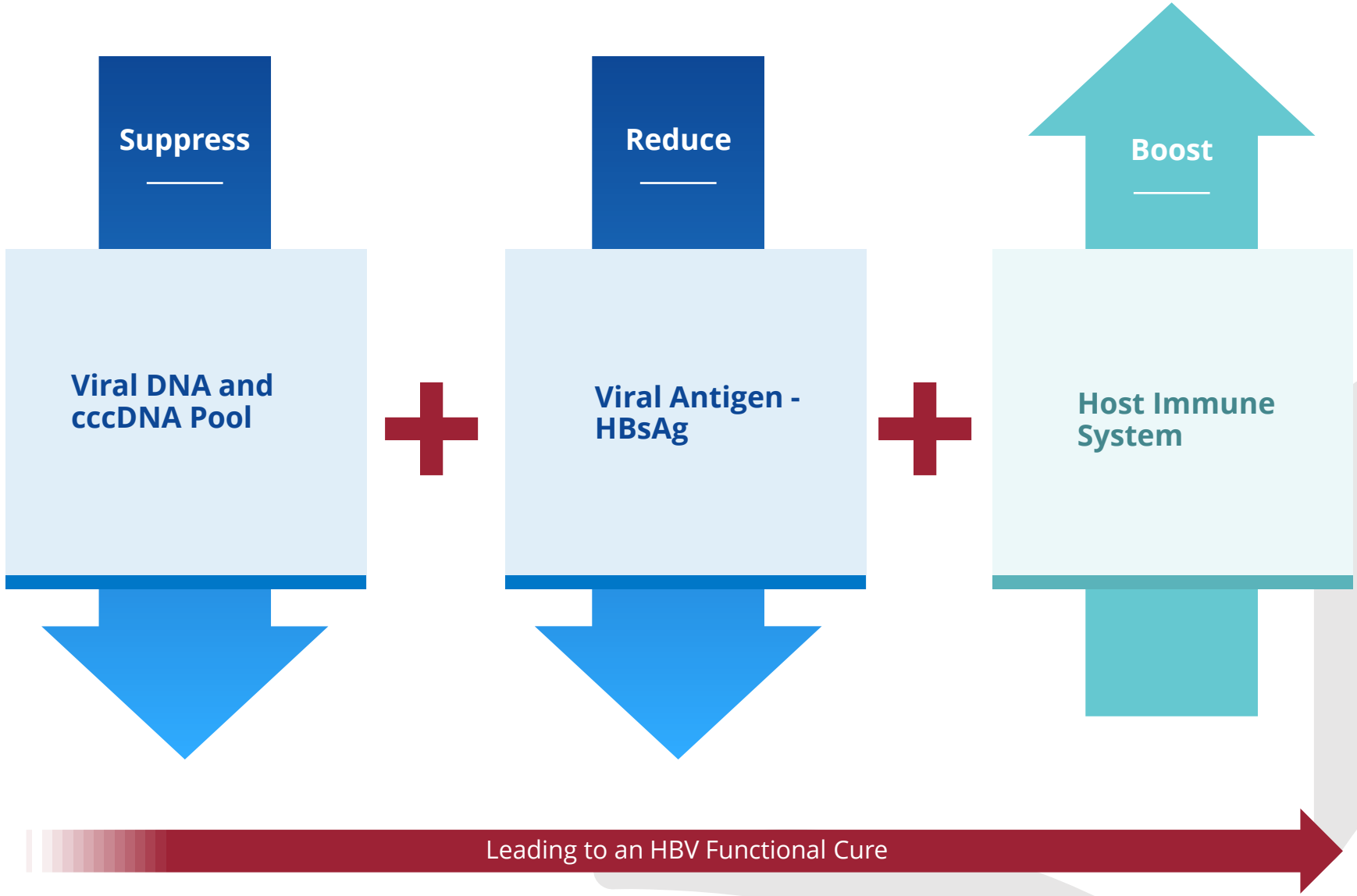
A Path to Therapeutic Success in HBV

- **Suppress** HBV DNA
- **Reduce** viral antigens
- **Boost** host immune response



Therapeutic success will **require a combination of agents** with complementary MOAs.

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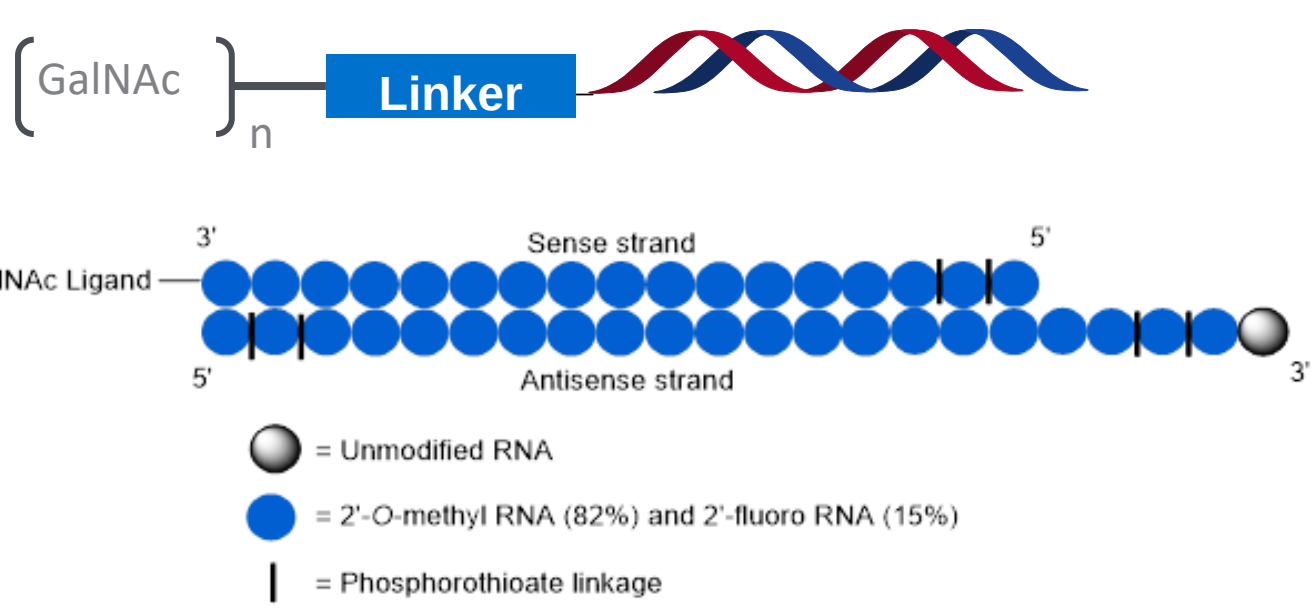
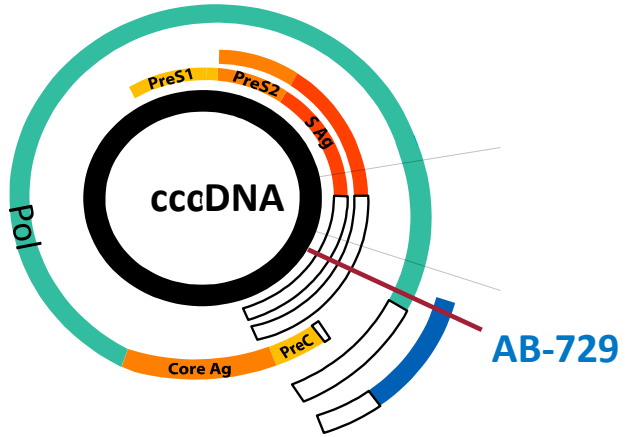
Imdusiran (AB-729): A Liver Targeted GalNAc Conjugated siRNA



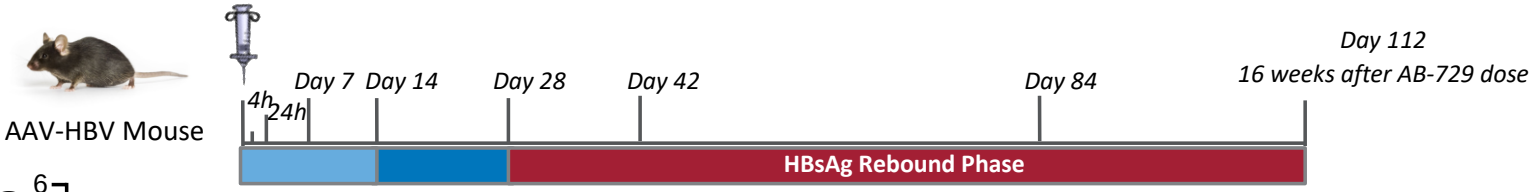


- Single trigger RNA interference agent
- Proprietary liver targeting technology based on GalNAc ligand interaction with ASPGR
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens, including HBsAg from integrated genome
- Broad genotype coverage and active against nucleoside resistant variants
- Long duration of activity from single SC dose

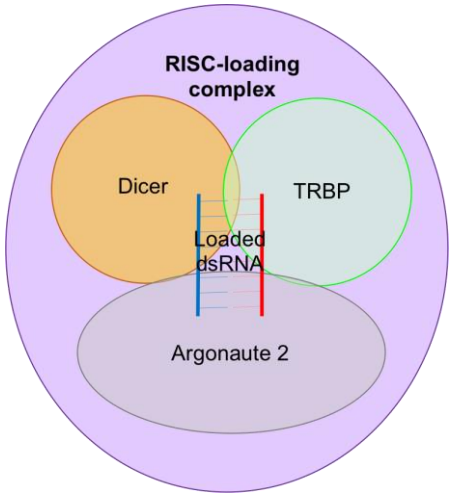
HBV Variant	HBsAg EC_{50} (nM)
Genotype A	11
Genotype B	40
Genotype C	59
Genotype D	62
ETVr L528M/M552V /T532G/S550I	61
TLVr M552V+L528M	89
ADVr A529V	143
Wildtype	73

PK Profile of RISC-Loaded AB-729 Antisense Strand in Liver Coincides with PD Profile of Serum HBsAg Reduction

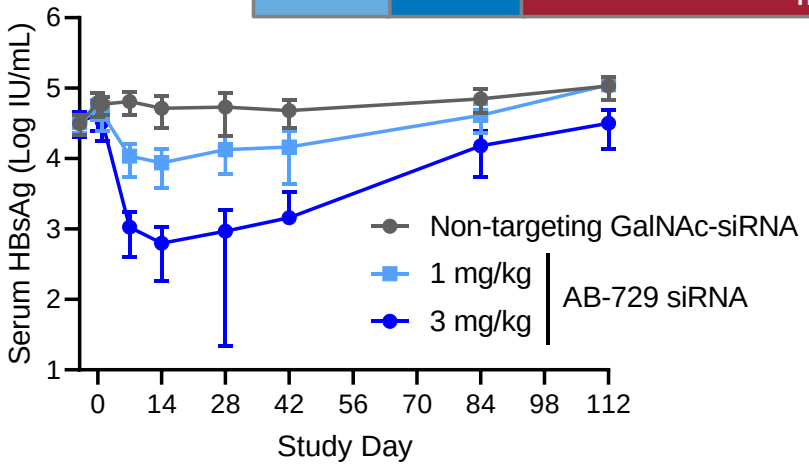
Single dose of AB-729 siRNA with surrogate GalNAc ligand at 1 mg/kg or 3 mg/kg
or non-HBV Targeting GalNAc-siRNA at 3 mg/kg
on Day 0

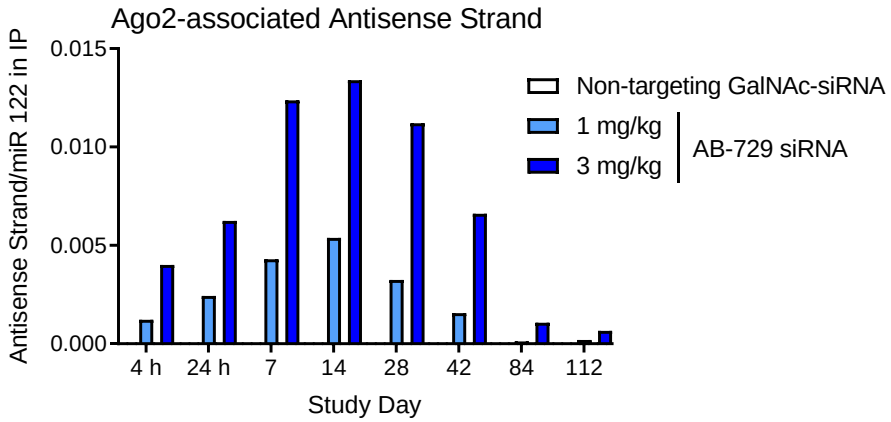


Analyses
- Serum HBsAg
- Total siRNA in liver
- Level of RISC-loaded siRNA



DICER – Rnase III endonuclease
TRBP - Protein with 3 dsRNA-binding domains
Argonaute 2 - RNase: catalytic center of RISC





- Degree of AB-729 antisense strand loading onto Ago2 in RISC complexes coincides with HBsAg reduction
- Ago2-associated AB-729 antisense strand increases over time, peaking at Day 14 and declining thereafter
- Peak of Ago2-associated AB-729 antisense strand at Day 14 coincides with nadir of HBsAg silencing
- Decline in Ago2-associated AB-729 antisense strand mirrors rebound in HBsAg observed after Day 28
- PK profile of RISC-loaded antisense strand is supportive of clinical dosing schedules being explored for AB-729 (Q4W, Q8W, Q12W)

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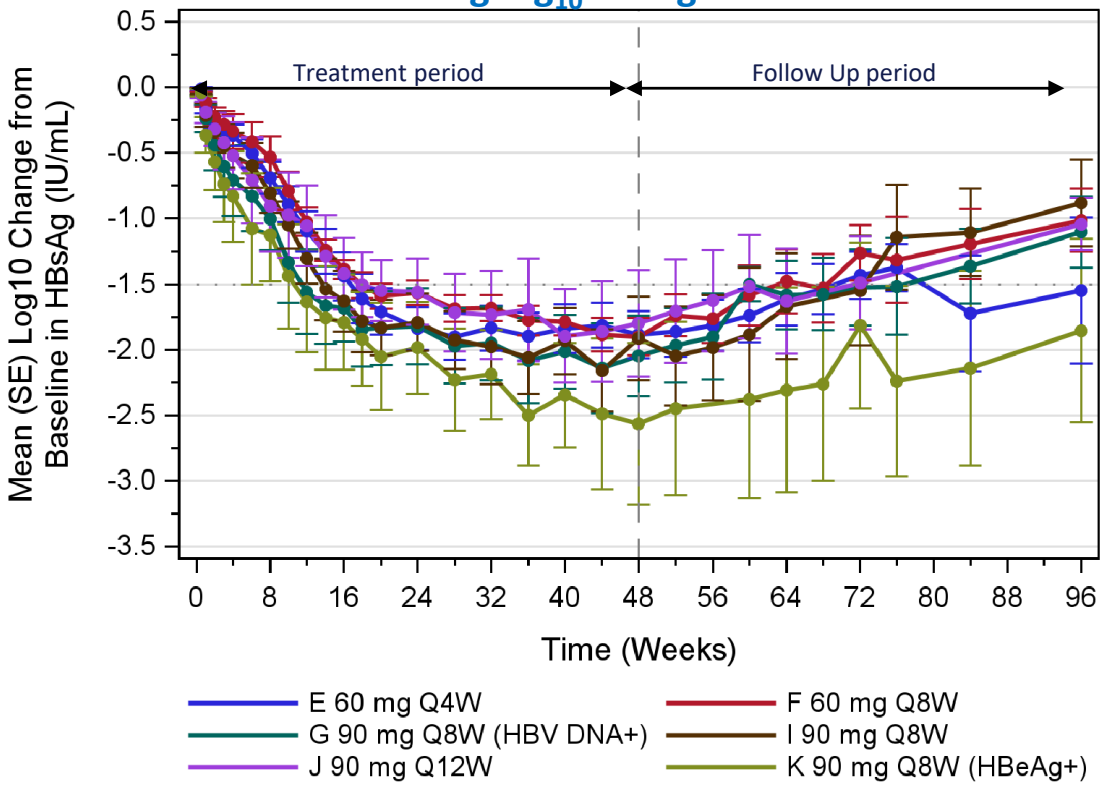
AB-729-001: Comparable mean HBsAg declines were observed in all Cohorts

Mean HBsAg log_{10} change from baseline



Mean HBsAg log_{10} IU/mL change from baseline at key timepoints

Visit	HBV DNA-					HBV DNA+
	Cohort E 60mg Q4W HBV DNA- (N=7)	Cohort F 60mg Q8W HBV DNA- (N=7)	Cohort I 90mg Q8W HBV DNA- (N=6)	Cohort J 90mg Q12W HBV DNA- (N=7)	Cohort K 90mg Q8W HBV DNA-, HBeAg+ only (N=7)	Cohort G 90mg Q8W + TDF (N=7)
Baseline	3.51 (0.20)	3.53 (0.17)	3.36 (0.23)	3.37 (0.28)	3.23 (0.14)	3.14 (0.14)
Treatment Week 12	-1.10 (0.15)	-1.02 (0.11)	-1.30 (0.19)	-1.06 (0.31)	-1.63 (0.39)	-1.56 (0.32)
Treatment Week 24	-1.84 (0.16)	-1.57 (0.09)	-1.79 (0.22)	-1.56 (0.25)	-1.99 (0.35)	-1.82 (0.29)
Treatment Week 48	-1.89 (0.18)	-1.90 (0.14)	-1.91 (0.32)	-1.80 (0.41)	-2.57 (0.61)	-2.05 (0.31)
Follow Up Week 12	-1.74 (0.20)	-1.59 (0.23)	-1.42 (0.26)	-1.52 (0.40)	-2.38 (0.75)	-1.50 (0.13)
Follow Up Week 24	-1.43 (0.18)	-1.26 (0.21)	-1.37 (0.39)	-1.49 (0.35)	-1.82 (0.63)	-1.53 (0.29)
Follow Up Week 48	-1.55 (0.56)	-1.01 (0.24)	-0.88 (0.33)	-1.04 (0.20)	-1.86 (0.70)	-1.10 (0.27)

Data shown are for a minimum of 5 subjects/timepoint. Last dose of AB-729: Cohort E, Week 44; Cohorts F, I, G, K: Week 40; Cohort J: Week 36.

- All Cohorts achieved at least a -1.8 log_{10} decline in mean HBsAg at the end of the treatment period (Week 48)
- There were no significant differences in mean HBsAg declines between the 60 mg and 90 mg doses or between different dosing intervals
- Mean HBsAg levels remained below baseline values at Week 48 Follow Up
- AB-729 was well-tolerated at all dose levels and intervals, with no discontinuations due to AEs or treatment-related Grade 3 or 4 AEs

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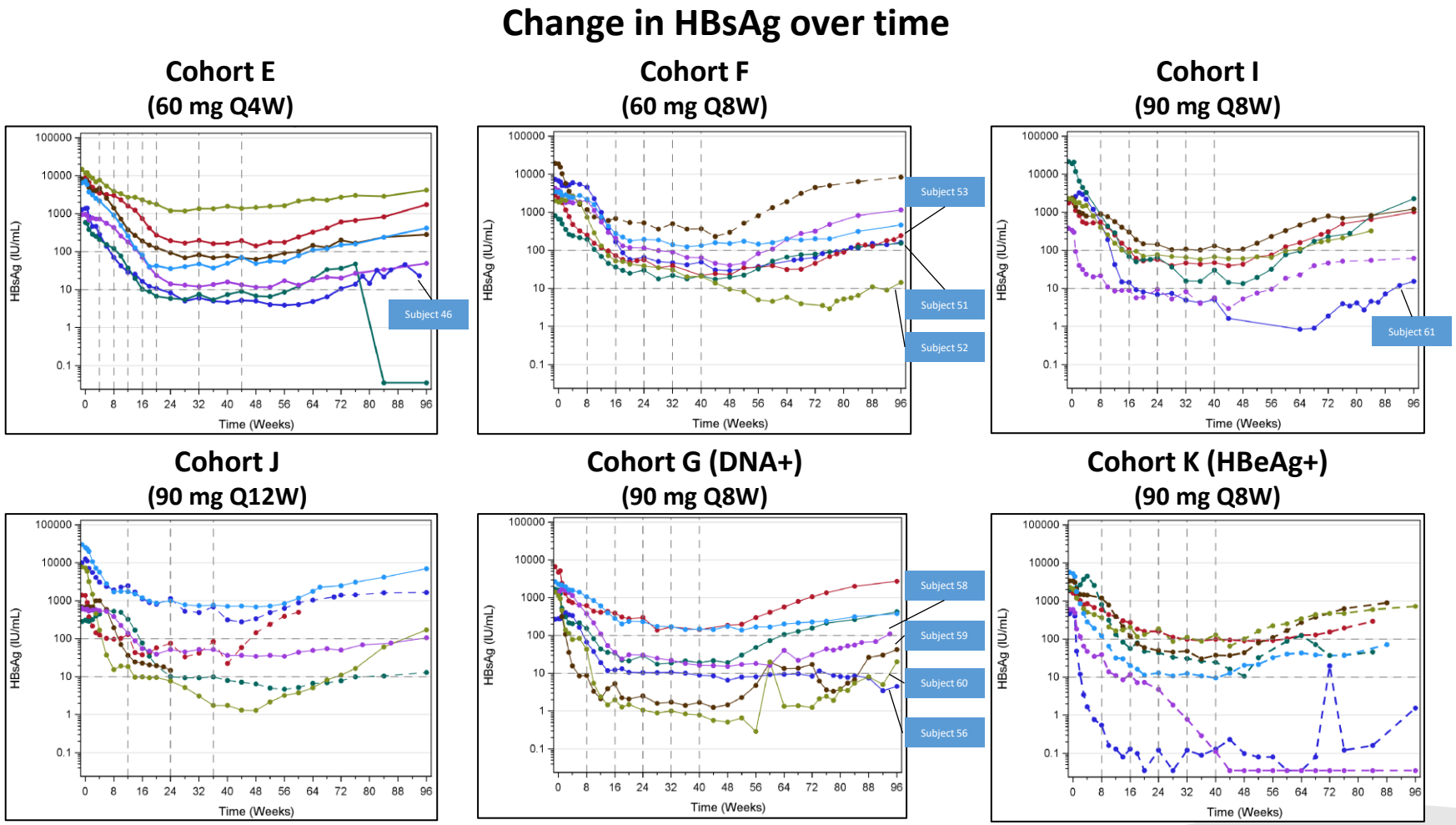
AB-729-001: Robust & Sustained HBsAg Declines While On- or Post-Treatment with Imdusiran



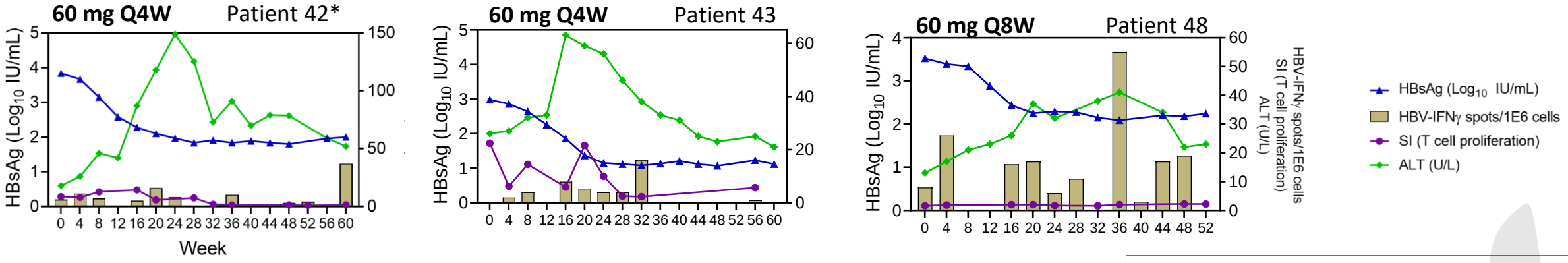
- 33 of 41 patients had HBsAg <100 IU/mL at some point during the trial
- 1 patient in Cohort E (baseline HBsAg = 583.5 IU/mL) who qualified but declined to participate in NA discontinuation seroconverted at Week 84 (HBsAg < LLOQ and HBsAb = 189 IU/mL at last visit); liver enzymes remained within normal limits
- 2 patients in Cohort K reached HBsAg <LLOQ on multiple visits with detectable HBsAb levels, 1 also reached HBeAg <LLOQ
- 9 patients qualified for NA discontinuation

Data presented at EASL 2022, AASLD 2022, GHS 2023

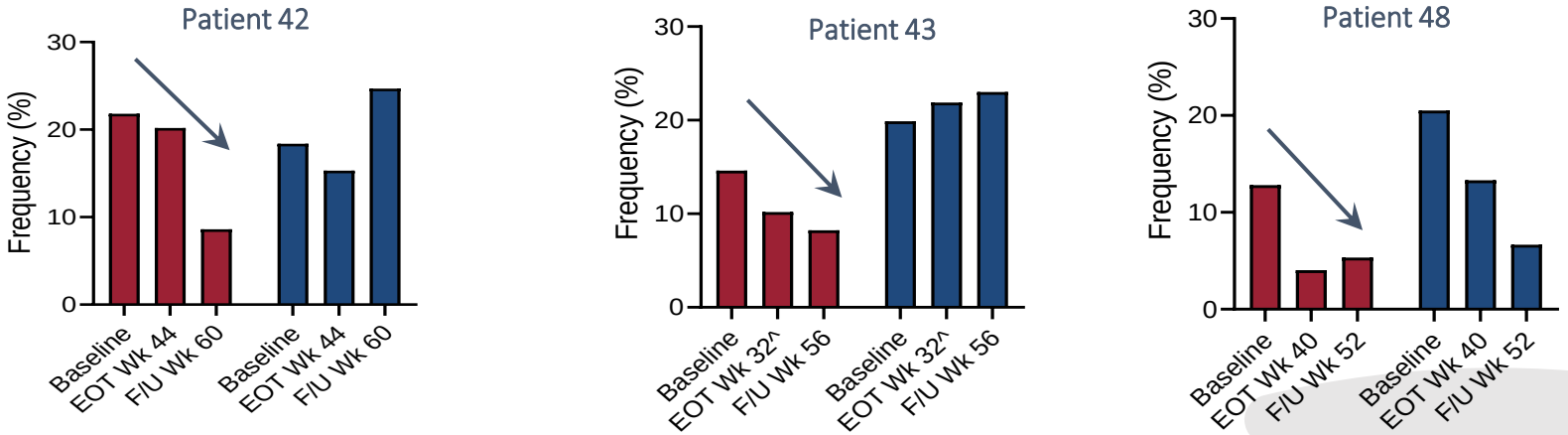
NA discontinuation criteria (determined at least 24 weeks post AB-729 cessation):
ALT <2x ULN, undetectable HBV DNA, HBeAg negative, and HBsAg <100 IU/mL at 2 consecutive visits

AB-729-001: Treatment with Imdusiran Induces HBV Specific Immunity in Some Patients

AB-729 Increased HBV-Specific T-Cell Activation



AB-729 Decreased Exhausted T-Cells



^ Last on-treatment PBMC sample available prior to last dose at Wk 44

- Upregulation of HBV-specific T-cell activation markers observed in all 7 patients assessed to date
- Two profiles of HBV-specific T cell IFN-γ responses observed
  - Elevation between Wk 16-28 which coincides with nadir of HBsAg reduction
  - *Elevation after AB-729 dosing completed, between Wk 48-60
- Reduction of global exhausted T cells also evident

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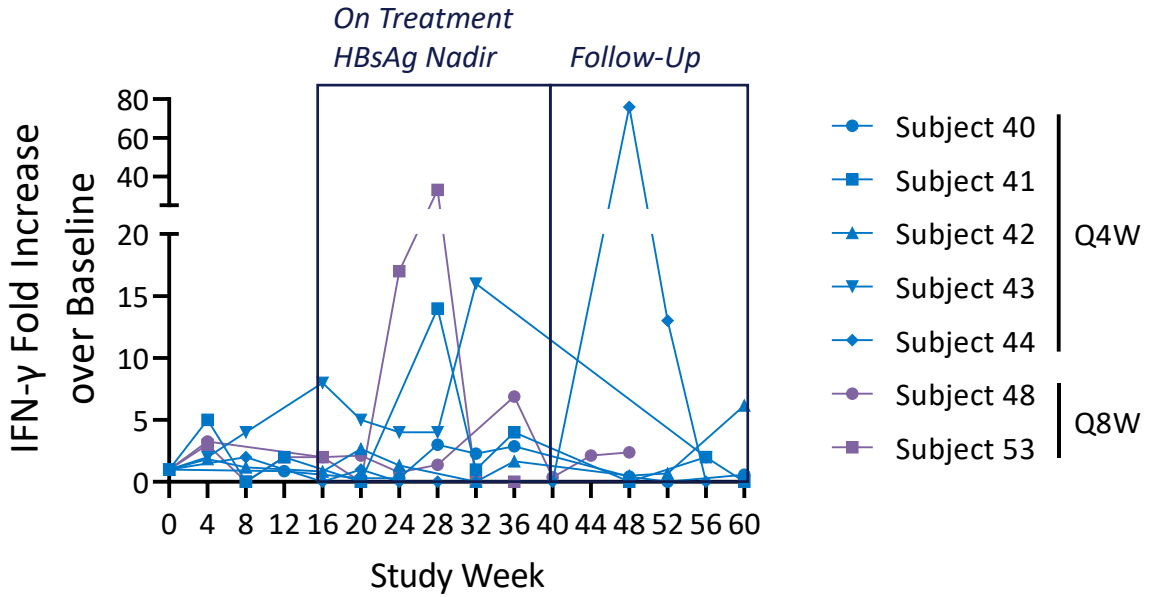
Data presented at EASL 2022

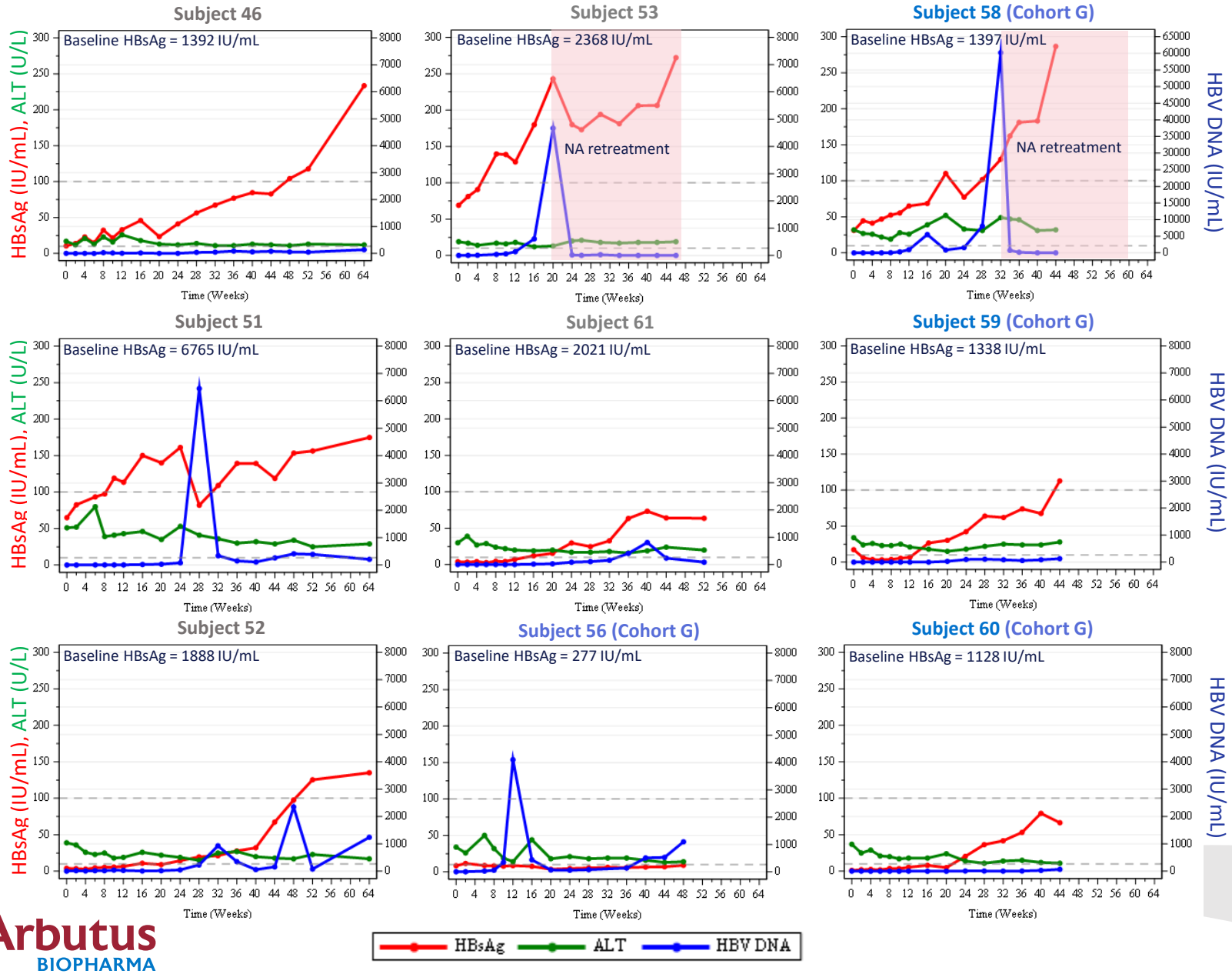
HBV-Specific T Cell Activation Markers are Upregulated in CHB Subjects Undergoing Imdusiran Dosing



- Two profiles of HBV-specific T cell IFN-γ responses observed
  - Elevation **during AB-729** dosing, which coincides with nadir of HBsAg reduction
  - Elevation **after AB-729** dosing completed, between Week 48-60

Subjects assessed to date for whom PBMC samples were available

HBV DNA suppression after NA cessation suggests immune control



- NA discontinuation post-imdusiran treatment appears well tolerated with no ALT flares
- Most subjects have maintained low HBV DNA levels off treatment, despite occasional blips
- Different profiles between HBV DNA and HBsAg suggest HBsAg is from integrated HBV DNA, not active viral replication

Time = weeks post-NA discontinuation; Time 0 is at least 24 weeks after last AB-729 dose

HBsAg LLOQ = 0.07 IU/mL, <LLOQ defined as 0.035 IU/mL

HBV DNA LLOQ = 10 IU/mL, <LLOQ defined as 5 IU/mL and TND defined as 1 IU/mL

ALT ULN = 48 U/L (males) or 43 U/L (females)

Dashed lines represent HBsAg of 100 IU/mL and 10 IU/mL

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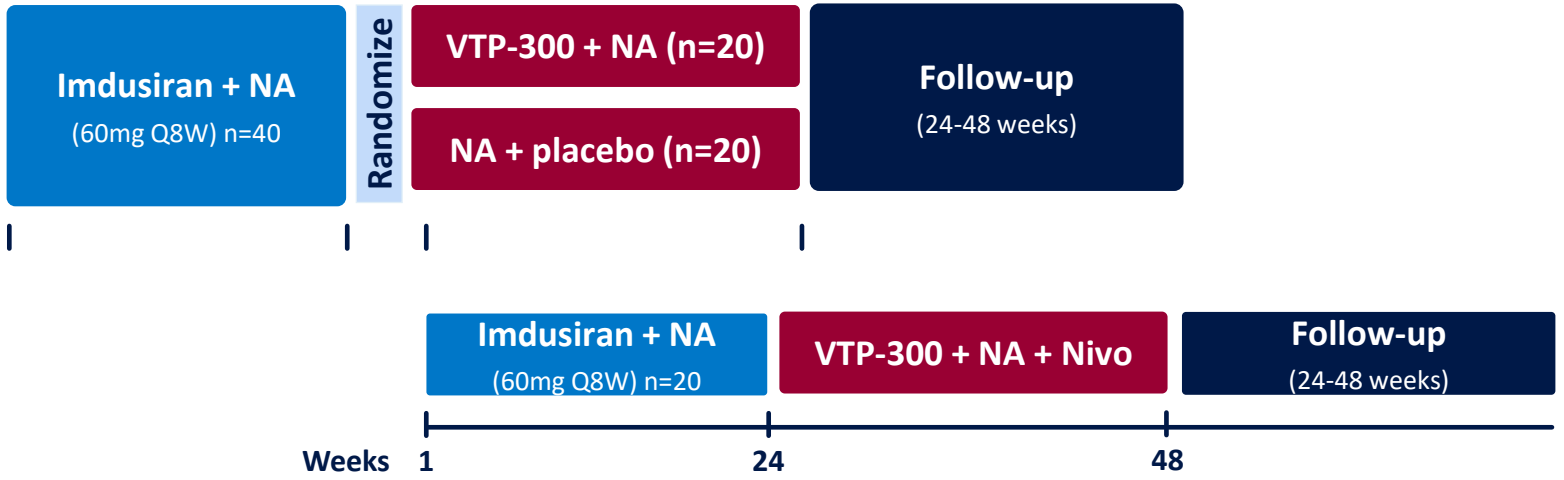
Combination Studies: Imdusiran + Immune Activation

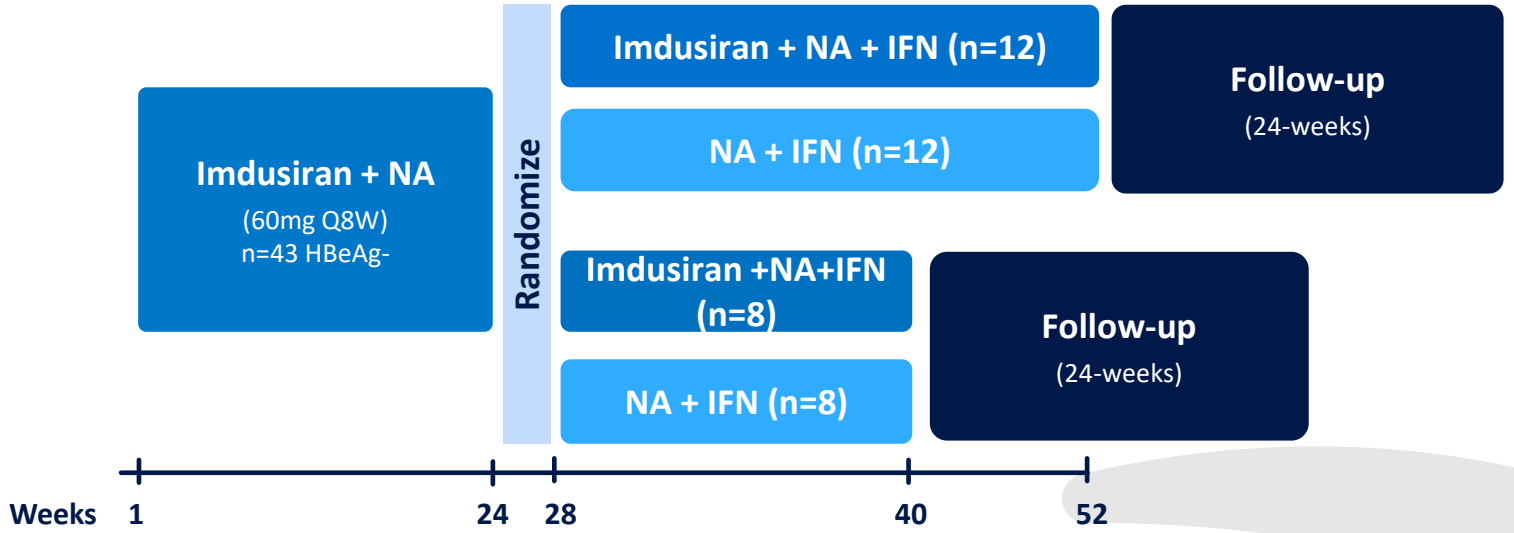
Imdusiran + Therapeutic Vaccine



2023 AASLD
LB Poster #5036-C

Preliminary pharmacodynamics and safety of repeat dosing of imdusiran (AB-729) followed by VTP-300 or placebo in virally-suppressed, non-cirrhotic subjects with chronic hepatitis B (CHB)

Imdusiran + IFNα



2023 EASL
LB Poster-38

Preliminary safety and antiviral activity of AB-729 combination treatment with pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection

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Conclusions

- AB-729 treatment produced robust and comparable declines in HBsAg regardless of dose, dosing interval, baseline HBeAg or HBV DNA status
- HBsAg declines in most subjects persist for at least a year after the last dose of AB-729
- Discontinuation of all therapy in AB-729-treated subjects who achieved HBsAg <100 IU/mL has led to continued low levels of HBV DNA and HBsAg in most subjects
  - No ALT flares have been observed
  - These results suggest ongoing host immune control in the absence of therapy
  - Subjects will be followed for up to 3 years to monitor for functional cure
- Immune profiling appears to show HBV-specific immune reactivation occuring in some patients
- AB-729 is in Phase 2 clinical development in combination with other agents, including pegylated interferon alfa-2a (NCT04980482) and VTP-300, a therapeutic vaccine (ACTRN12622000317796).
- Additional supportive data on immune reactivation with Imdusiran in combination with VTP-300 will be presented at AASLD 2023 (LB # 5036-C)

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Acknowledgements

Imdusiran Discovery and Development Teams

We thank all patients and study investigators

Thank You