Imdusiran Combinations Achieving HBsAg Loss

International Workshop on HBV Cure

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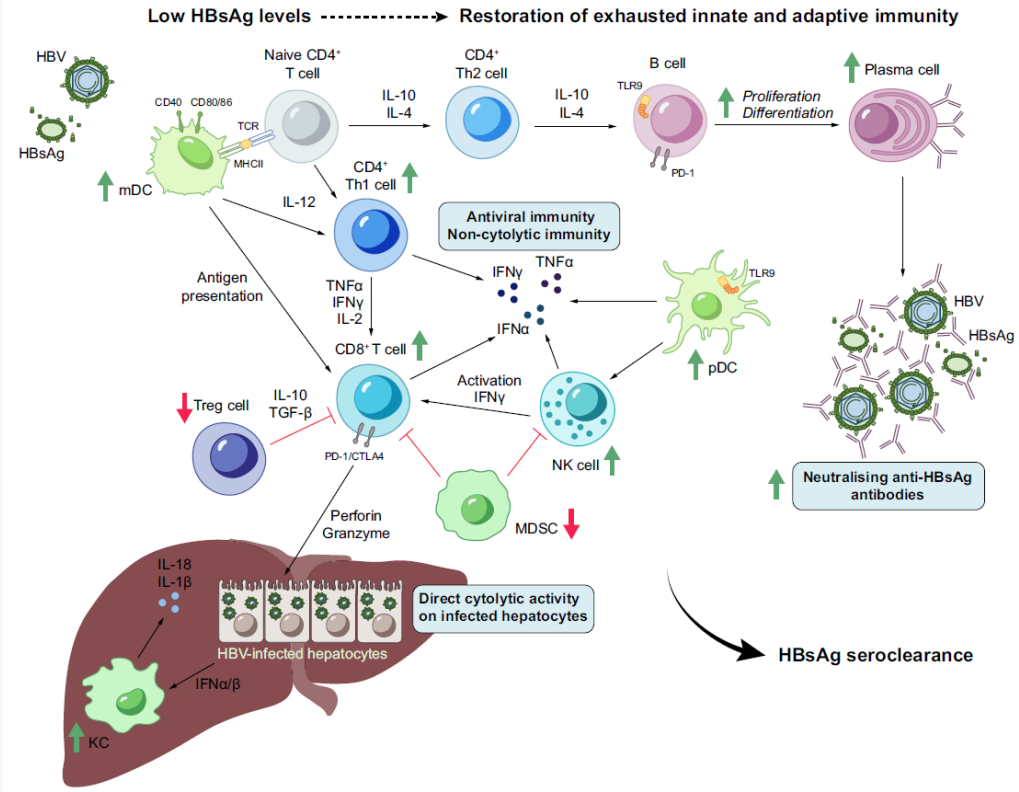
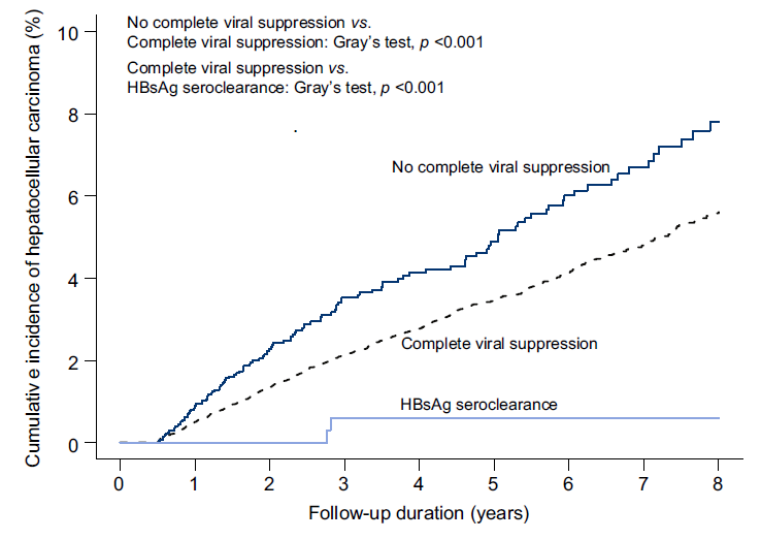
Disclosures – Karen Sims, MD/PhD

I am an employee and shareholder of Arbutus Biopharma.

Why is HBsAg loss important?

- Circulating HBsAg contributes to immune exhaustion in cHBV patients
- HBsAg seroclearance may decrease risk of future HCC, cirrhosis and fibrosis progression
- Low HBsAg levels are predictors for functional cure
  - Discontinuation of NA therapy in clinical practice more successful when HBsAg levels are <1000 IU/mL or <100 IU/mL
  - Recent clinical trials show higher rates of HBsAg loss in subjects with baseline HBsAg <3000 IU/mL or <1000 IU/mL





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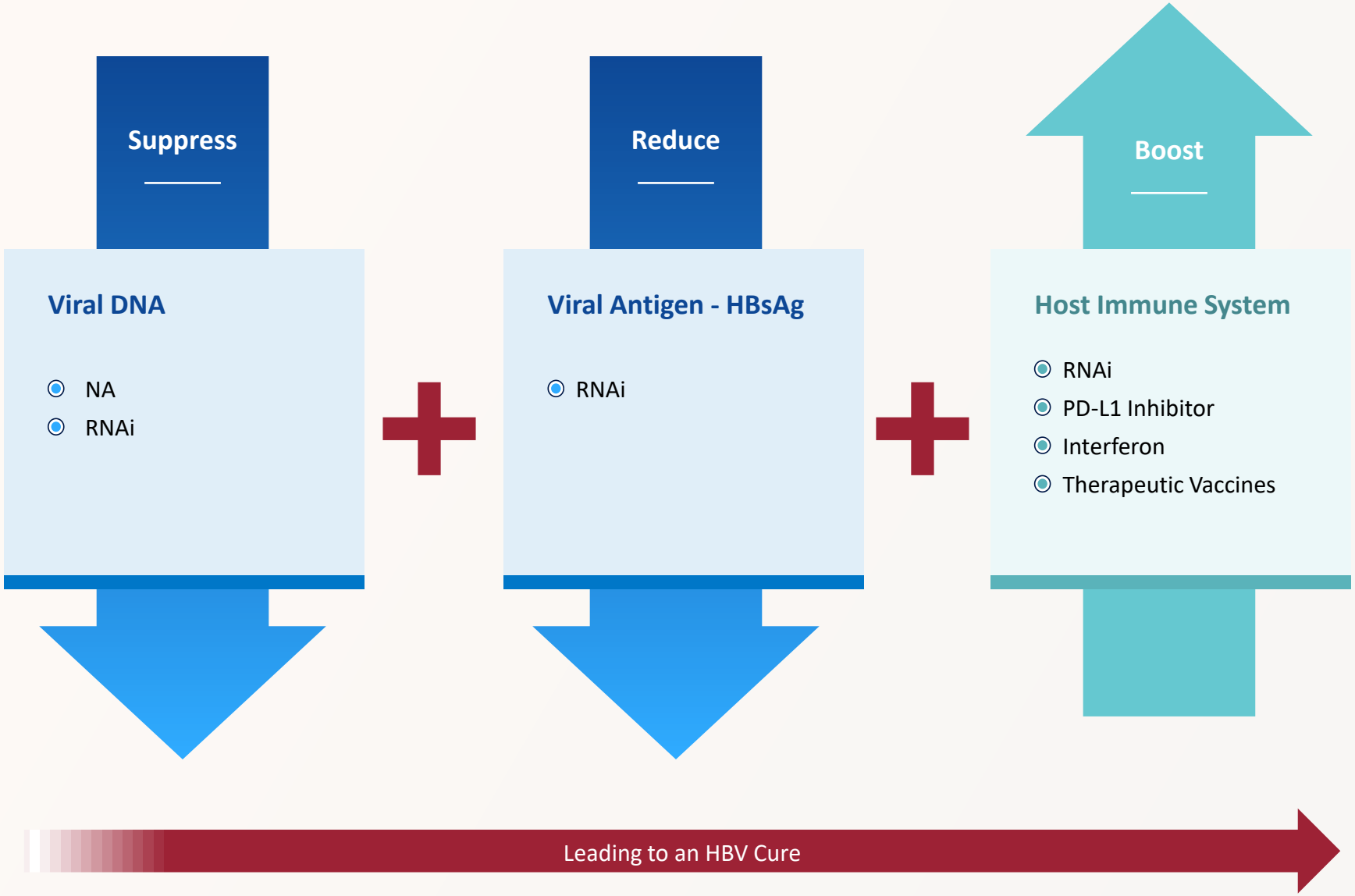
3-Pronged Approach to Therapeutic Success

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

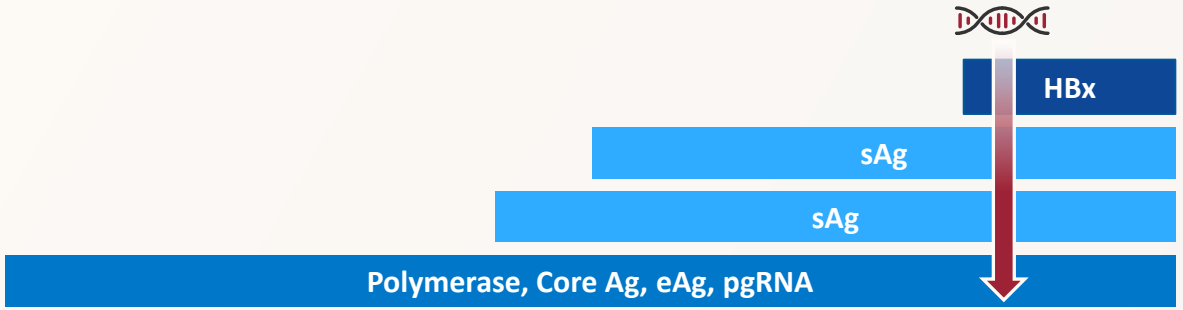


Therapeutic success will **require a combination of agents** with complementary MOAs.

Imdusiran (AB-729)

Proprietary GalNAc-conjugate delivery technology provides liver targeting and enables **subcutaneous dosing**

- Single trigger RNAi agent targeting all HBV transcripts including HBx
- Inhibits HBV replication and lowers all HBV antigens
- Pan-genotypic activity across HBV genotypes including A – E in the clinic
- Demonstrated complementarity with other agents
- Actively targets the liver
- Active against cccDNA derived and integrated HBsAg transcripts
- Favorable profile in long term preclinical safety and clinical studies



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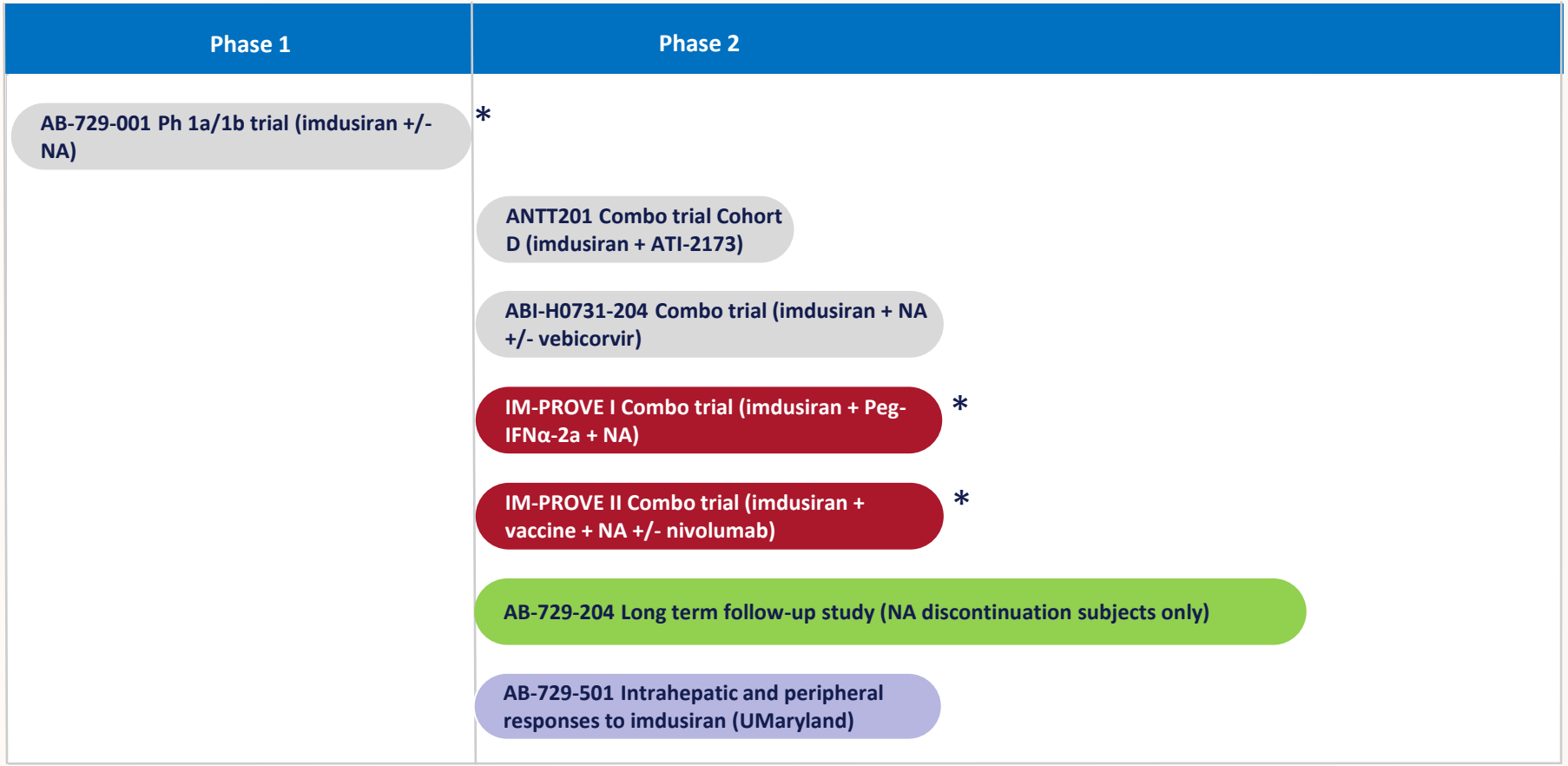
Imdusiran Clinical Trials to date



* HBsAg loss observed

- Red bars indicate trials with the addition of an immunomodulator (IFN, VTP-300 with or without low does nivolumab)

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AB-729-001 Phase 1a/1b Clinical Trial

Part 1 & 2:

Single-ascending dose

Imdusiran single dose conclusions:

- Robust HBsAg declines across all cohorts
- HBV DNA declines in HBV DNA+ patients

Part 3: Multiple Ascending Dose in cHBV Patients

E: 60mg Q4W
HBV DNA-

F: 60mg Q8W
HBV DNA-

G: 90mg Q8W + TDF
HBV DNA+

I: 90mg Q8W
HBV DNA-

J: 90mg Q12W
HBV DNA-

K: 90mg Q8W HBV DNA-
HBeAg+ only

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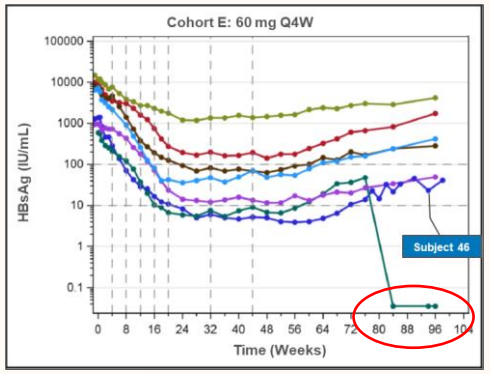
HBeAg: HBV E antigen | **TDF:** tenofovir disoproxil fumarate

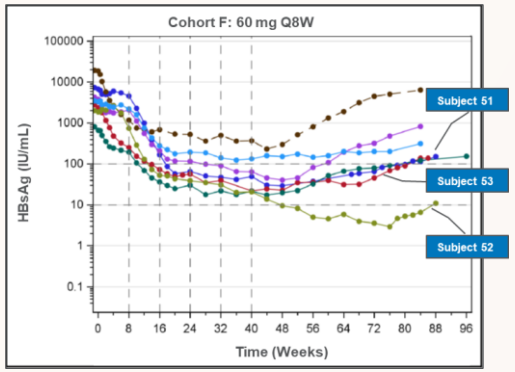
AB-729-001: HBsAg loss is possible with imdusiran + NA alone

Change in HBsAg vs time

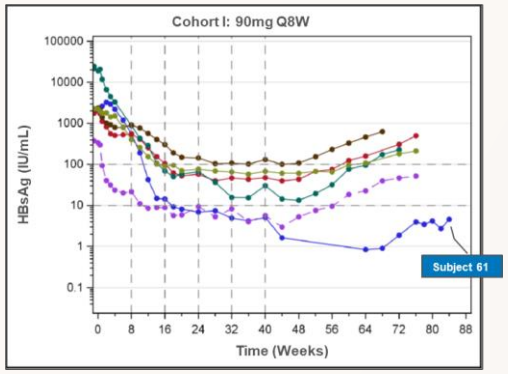
Cohort E



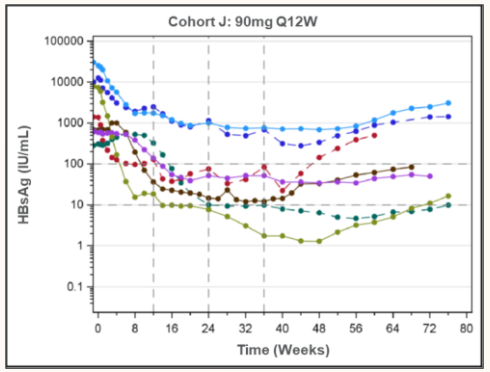
Cohort F



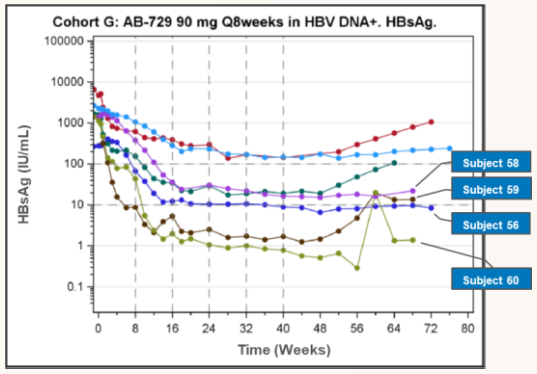
Cohort I



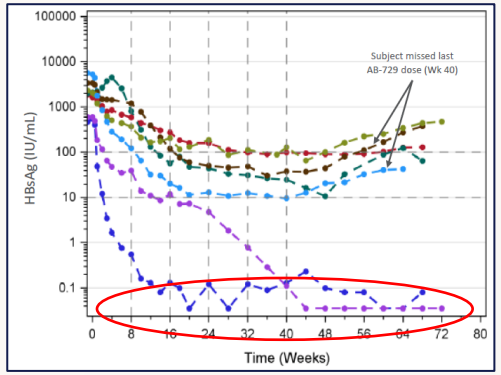
Cohort J



Cohort G (DNA +)



Cohort K (HBeAg+)



- 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
- All patients with HBsAg loss had baseline HBsAg <1000 IU/mL
- Time course to HBsAg loss is prolonged without an additional agent

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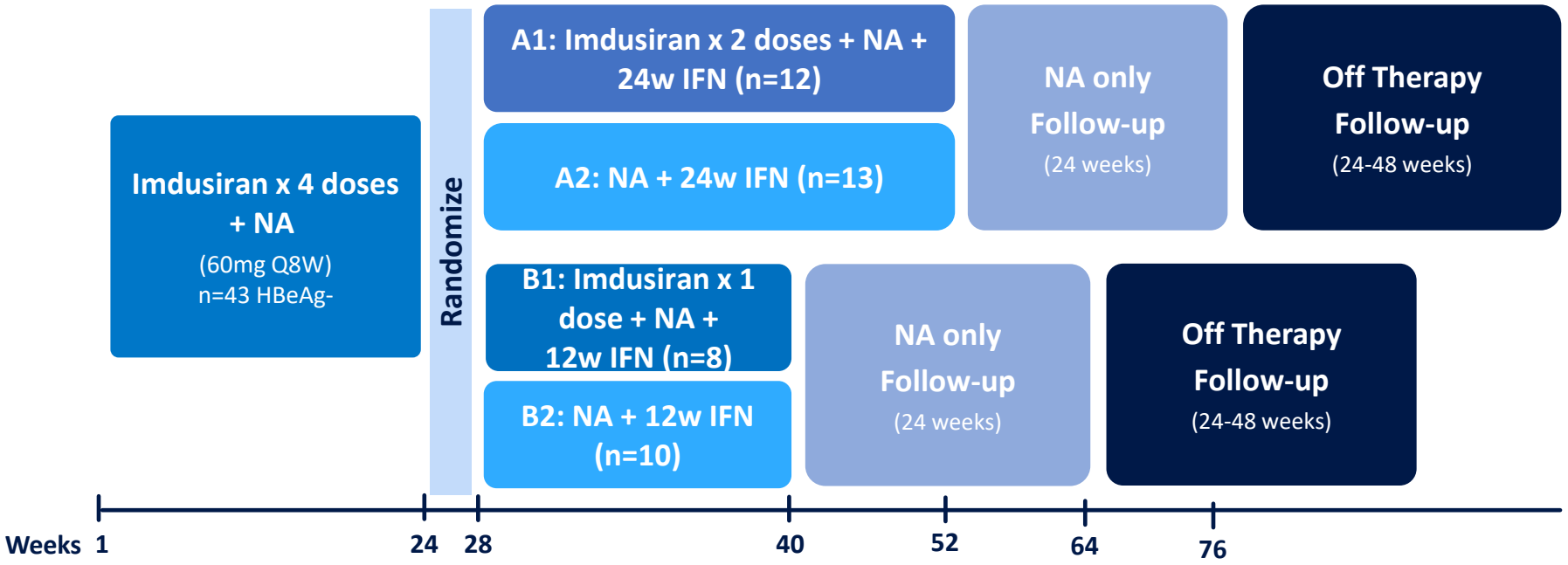
Data presented at EASL 2022 and AASLD 2022

IM-PROVE I:

Phase 2a POC Clinical Trial

Imdusiran in combination with **ongoing NA therapy and short courses of Peg-IFNα-2a in cHBV patients**



Multi-center, open-label Phase 2a

Primary objective: evaluate safety and tolerability of imdusiran in combination with Peg-IFNα-2a in patients with NA-suppressed cHBV

After completing IFN treatment and the 24-week NA only follow-up period, patients who meet the criteria to discontinue NA therapy will be followed for an additional 48 weeks off therapy

Data presented at EASL Congress 2024 showed that 48 weeks of imdusiran plus 24 weeks of IFN therapy was generally safe, well-tolerated and achieved sustained HBsAg loss in 33% of patients after completion of IFN treatment, which was maintained in 100% of these patients 24 weeks after completing imdusiran and IFN treatment

Functional cure data to be presented at AASLD – The Liver Meeting 2024 **(Late breaker poster #5036)**

POC: Proof of Concept

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POC: Proof of Concept

IM-PROVE I: Imdusiran with Short Courses of IFN Leads to Sustained HBsAg Loss

Achieved HBsAg loss (≤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
Anytime during treatment:				
All	6/12 (50%)	3/13 (23%)	2/8 (25%)	0/10
BL HBsAg <1000 IU/mL	4/6 (67%)	2/7 (29%)	1/6 (17%)	0/4
EOT:				
All	4/12 (33%)	3/13 (23%)	0/8	0/10
BL HBsAg <1000	4/6 (67%)	2/7 (29%)	0/6	0/4
24W post-EOT:				
All	4/12 (33%)	2/13 (15%)	0/8	0/10
BL HBsAg <1000	4/6 (67%)	2/7 (29%)	0/6	0/4
Functional Cure:				
All	See AASLD LB poster #5036	See AASLD LB poster #5036	0/8	1/10 (10%)
BL HBsAg <1000			0/6	0/4

IDR: imdusiran; W: week; EOT: end-of-treatment

Key Findings:

- Subjects with baseline HBsAg <1000 IU/mL more likely to achieve HBsAg loss
- Patients with sustained HBsAg loss had corresponding high anti-HBs levels (43.8 to >1000 mIU/mL)
- Imdusiran and 24 weeks of IFN was generally safe and well-tolerated with no related SAEs and no AEs leading to discontinuation

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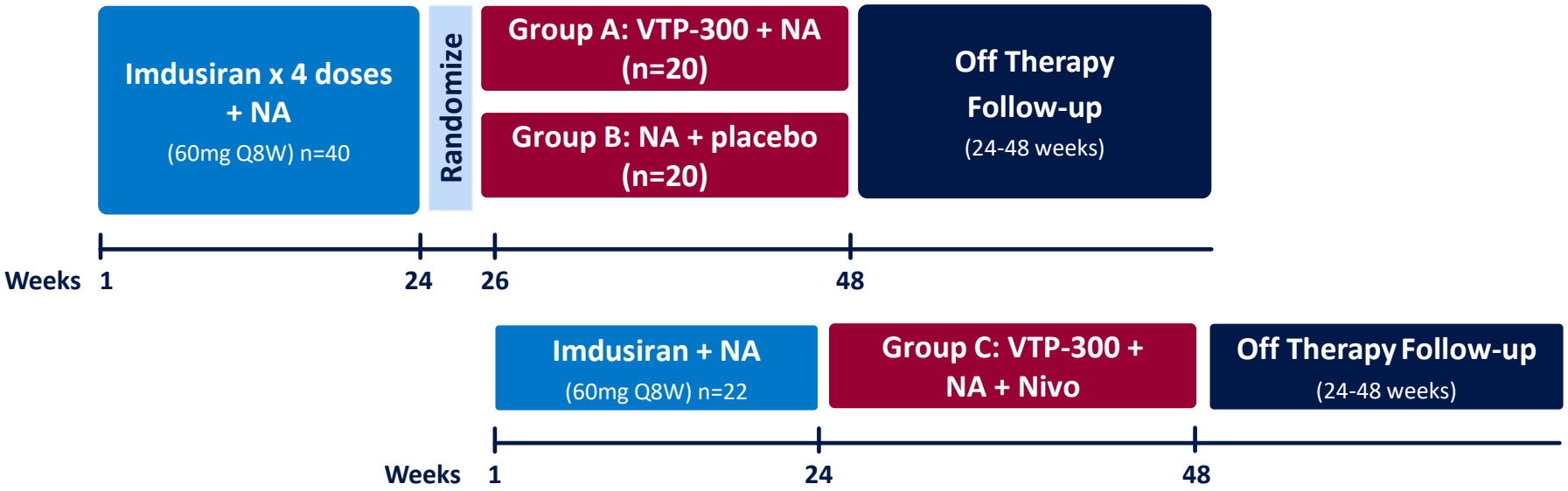
Data presented at EASL 2024

Functional Cure: sustained HBsAg loss and HBV DNA <LLOQ with or without anti-HBs that is maintained for 24 weeks after discontinuing all therapy.

IM-PROVE II:

Phase 2a POC Clinical Trial

POC Phase 2a clinical trial evaluating imdusiran in combination with Barinthus Bio's immunotherapeutic, VTP-300, and NA with or without low dose nivolumab



Multi-center, PBO controlled Phase 2a

Primary objective: evaluate safety and reactogenicity of imdusiran followed by VTP-300 or placebo

At Week 48 all participants who are eligible to discontinue NA therapy will be followed for an additional 48 weeks

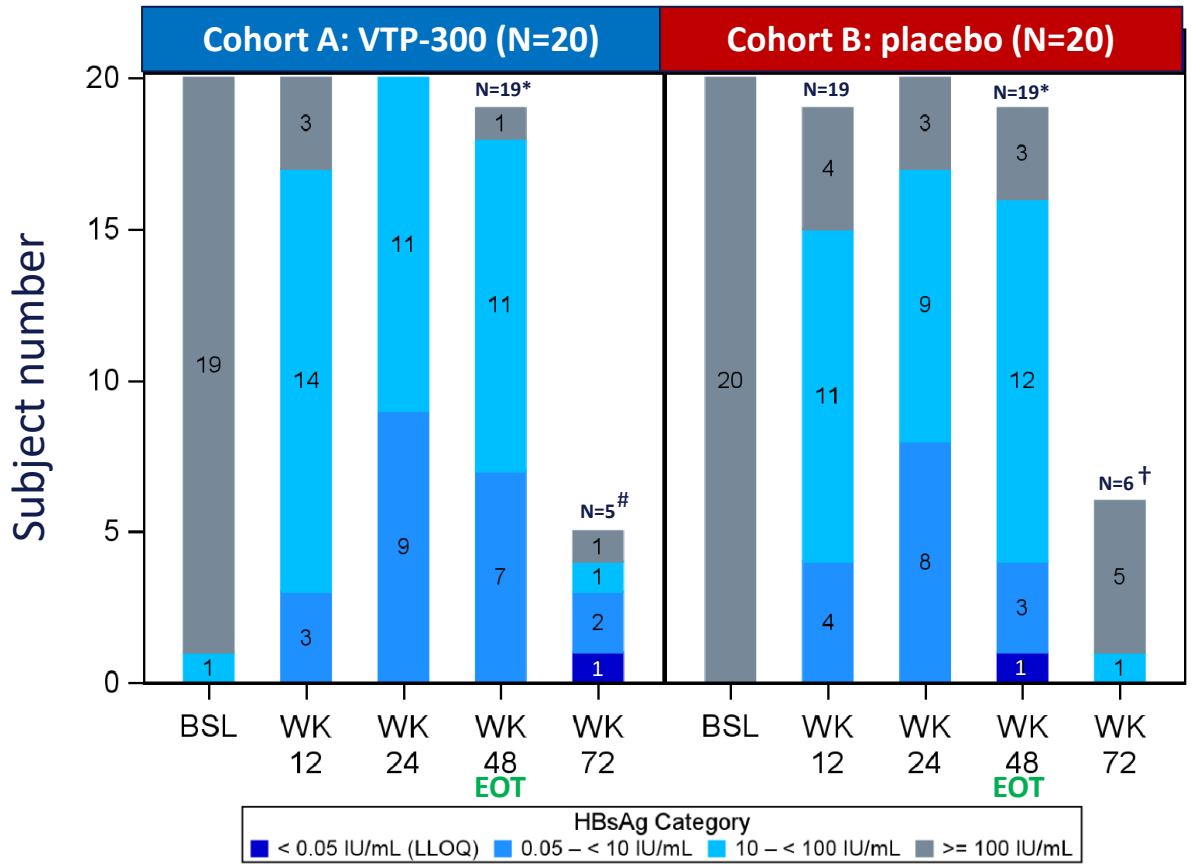
Results presented at EASL Congress 2024 showed that imdusiran followed by VTP-300 was generally safe and well-tolerated and led to maintenance of lower HBsAg levels during the post-treatment follow-up period

Clinical trial expanded to include an additional arm with nivolumab (Opdivo®) with preliminary data presented at AALSD – The Liver Meeting 2024 **(Late breaker poster #5025)**

POC: Proof of Concept

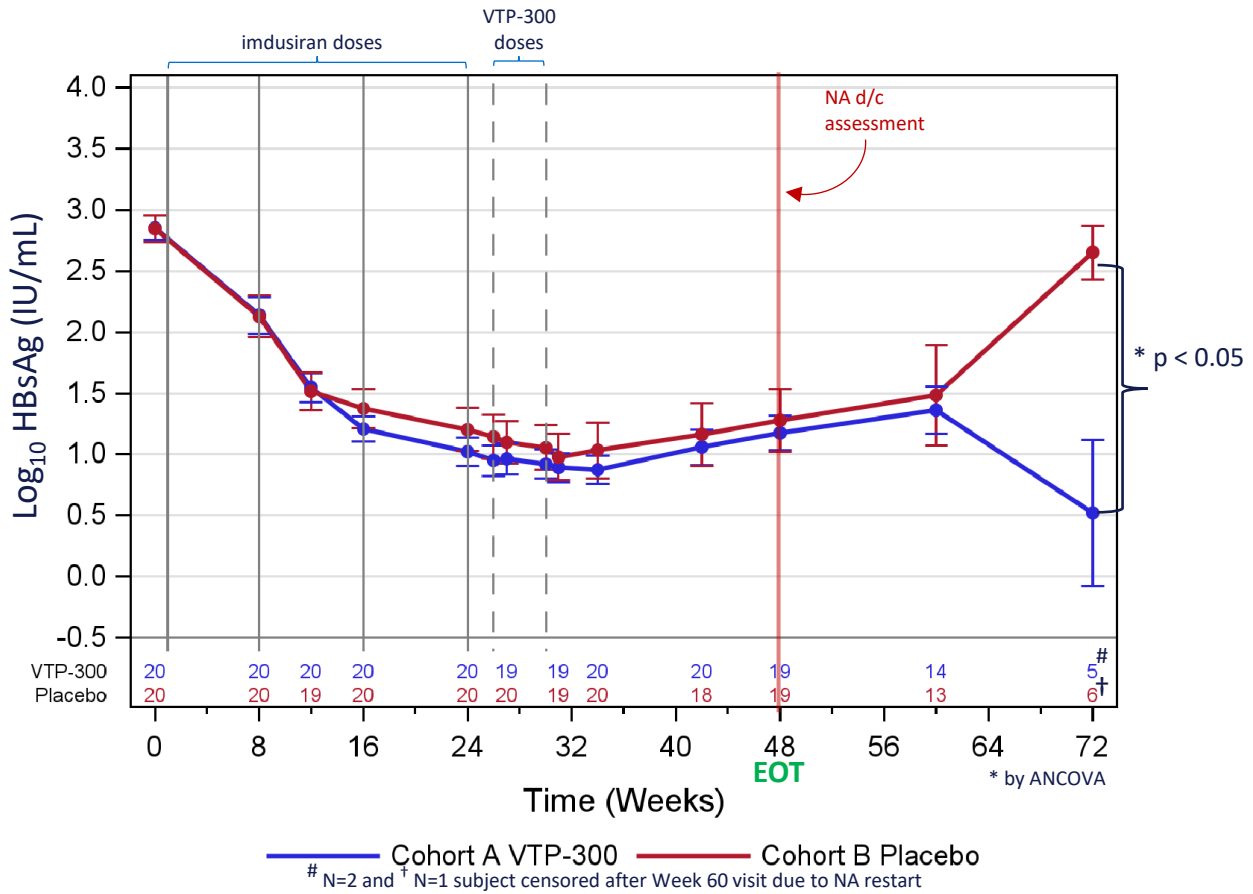
IM-PROVE II: Imdusiran and VTP-300 Achieve Statistical Significance in Lowering HBsAg Levels

HBsAg Thresholds Achieved by Visit



BSL=baseline; WK=week; EOT=end of treatment; * 2 subjects did not reach timepoint by datacut;
# N=2 and † N=1 subject censored after Week 60 visit due to NA restart

Mean [SE] Log_{10} HBsAg Level by Visit



N=2 and † N=1 subject censored after Week 60 visit due to NA restart

- At 24 weeks post-EOT (Week 72, N=11), there was a significant difference in HBsAg levels between groups, which may reflect the delayed effect of VTP-300 on HBsAg levels observed in other trials
- 2 subjects achieved HBsAg loss to date in Groups A&B; data for Group C with nivolumab to be presented at AASLD (LB poster 5025)
- 26/40 subjects discontinued NA therapy, and follow-up is ongoing to monitor for additional/sustained HBsAg loss

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Conclusions

- HBsAg loss is possible with siRNA monotherapy added to ongoing NA therapy, but at low rates
- Significant rates of HBsAg loss can be achieved with the addition of an immunomodulator to an siRNA-containing regimen
  - Deep suppression of HBsAg prior to adding the immunomodulator may be important to maximize efficacy
  - Short courses of pegylated interferon alfa-2α appear to have the best balance of efficacy and safety when added to an siRNA-containing regimen to date, with HBsAg loss rates of up to 67% in baseline HBsAg <1000 IU/mL
  - Exploration of other immunomodulator classes is ongoing
    - Checkpoint inhibitors may add similar benefit in selected populations, oral agents such as AB-101 may improve the safety profile vs antibodies and allow fine-tuning of checkpoint inhibition
    - Therapeutic vaccines remain under evaluation with/without additional immunomodulatory boosting (nivolumab, IFN)
- Additional data for imdusiran combinations will be presented at AASLD
  - Late breaker posters **5036** (IM-PROVE I with IFN) and **5025** (IM-PROVE II with VTP-300 and low dose nivolumab)
  - Posters **1383** (IM-PROVE I immune biomarker profiling) and **1391** (conservation of imdusiran target site variants)

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Acknowledgements

Arbutus Biopharma thanks all participating study subjects and their families, our Investigators and site staff, our IM-PROVE II collaborators Barinthus Biotherapeutics, our CRO and laboratory partners, and the imdusiran Research and Development Teams.

Thank you!

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