Imdusiran (AB-729) administered every 8 weeks for 24 weeks followed by the immunotherapeutic VTP-300 maintains lower HBV surface antigen levels in NA-suppressed CHB subjects than 24 weeks of imdusiran alone

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EASL CONGRESS 2024
Milan, Italy
5–8 June

Disclosures – Dr. Kosh Agarwal

- Consultancy: Aligos, ASC Therapeutics, Bluejay Therapeutics, DrugFarm, Gilead, GSK, Grifols, Janssen, PrecisionBio, Roche, Surrozen, Tune, Vir
- Grants: Gilead, GSK, Abbott

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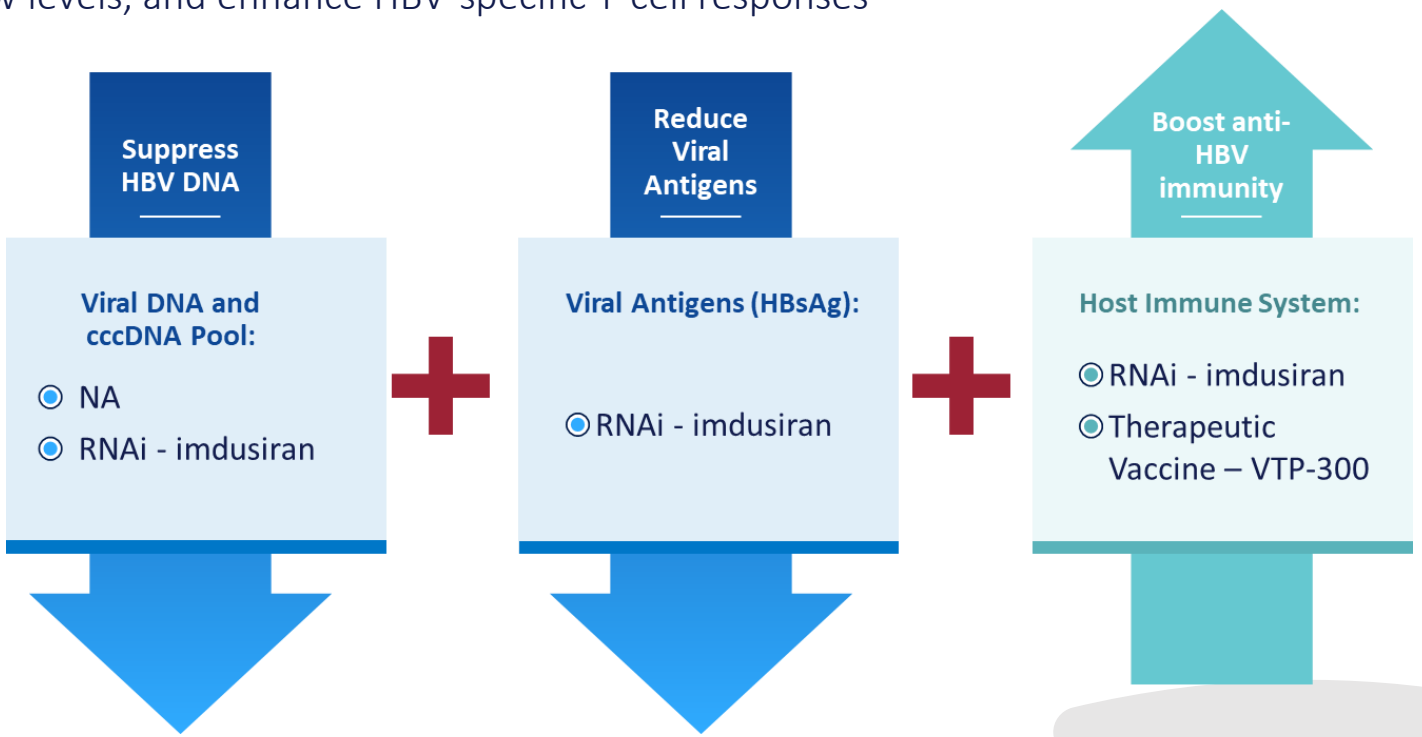
Background

- Current approved therapies for chronic hepatitis B (CHB) slow or prevent the development of HBV-related liver complications, but do not typically lead to functional cure (HBV DNA suppression and HBV surface antigen [HBsAg] loss, with or without HBsAb seroconversion at least 6 months off all treatment)[1-3]
- Excess production of HBsAg is believed to contribute to host immune exhaustion, resulting in inadequate T-cell and B-cell responses to CHB infection and failure to suppress the virus[4]
- Therapeutic success will require a combination of agents with complementary mechanisms of action to suppress HBV DNA, reduce HBsAg to low levels, and enhance HBV-specific T-cell responses



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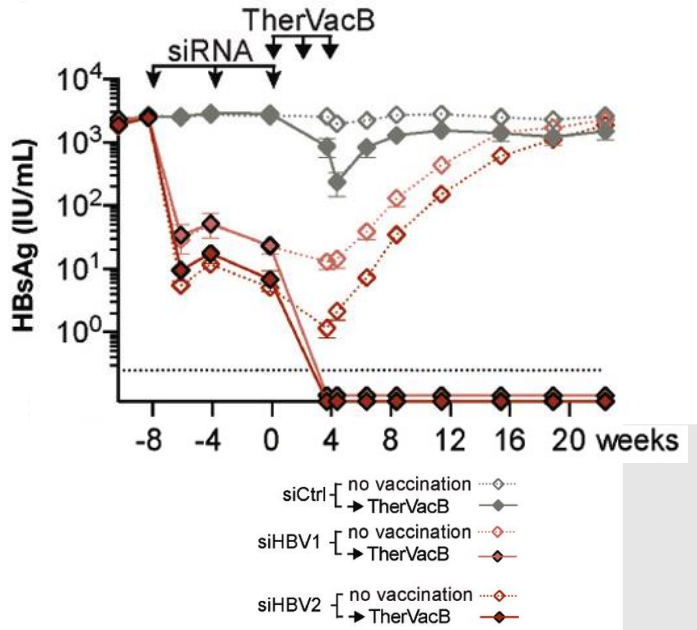
Study Rationale

- Preclinical data in the AAV-HBV mouse model supports lowering HBsAg with an siRNA then following with a therapeutic vaccine to potentiate HBsAg loss and T cell responses[1]
- Imdusiran for 24 weeks (to reduce HBsAg to low levels), followed by VTP-300 (to enhance HBV-specific T cell responses) in NA-suppressed CHB patients may promote HBsAg loss which may lead to functional cure
- **Imdusiran (AB-729/IDR)**[2-4]
  - GalNAc-conjugated, single trigger siRNA that blocks all HBV RNA transcripts (including HBx), suppressing viral replication and production of all viral antigens
  - Subcutaneously administered, 60 mg every 8 weeks
  - Lowers mean HBsAg levels by ~1.5 – 2 $\log_{10}$ after 24 – 48 weeks of treatment in combination with NA in multiple studies
- **VTP-300 immunotherapeutic**[5-7]
  - 2 viral vectors encoding the same consensus HBV viral sequences used in sequential combination:
    - Chimpanzee adenoviral vector (ChAdOx1-HBV)
    - Modified Vaccinia Ankara vector (MVA-HBV)
  - Generates robust T-cell responses and induces sustained HBsAg declines in a subset of subjects with low HBsAg (<200 IU/mL)
  - Maximal effects on HBsAg reduction observed at least 3 months after dosing



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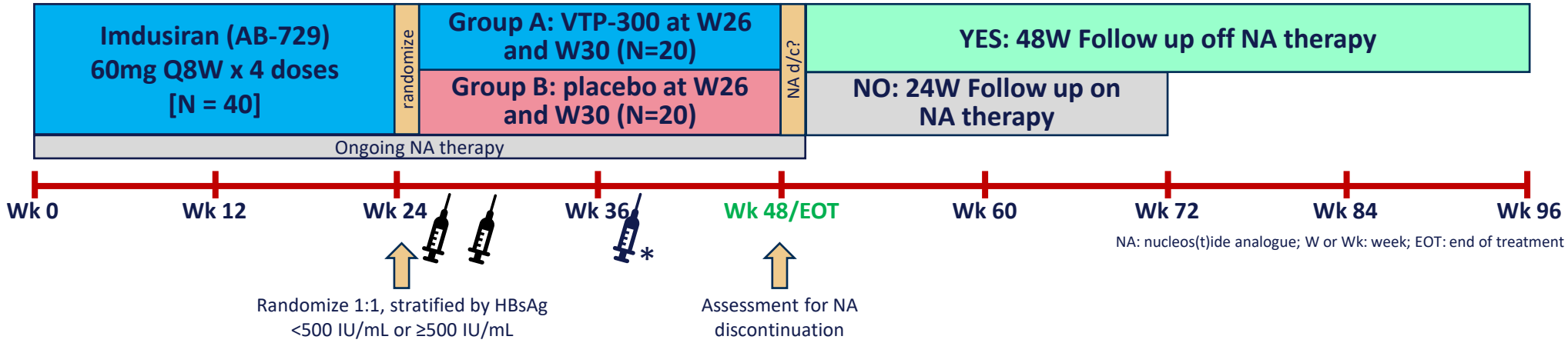
Study overview: IM-PROVE II (AB-729-202)

- IM-PROVE II is a randomized, placebo-controlled, multicenter Phase 2a proof-of-concept study (ACTRN12622000317796)
- Primary Objective: To evaluate the safety and reactogenicity of the combination of imdusiran followed by VTP-300 or placebo injection
- Week 48/EOT data is reported for 38/40 subjects who reached timepoint, data to Week 72 and beyond reported as available*



NA: nucleos(t)ide analogue; W or Wk: week; EOT: end of treatment

Study population:

- NA-suppressed for at least 12 months with HBV DNA < 20 IU/mL
- HBeAg-positive or -negative
- HBsAg ≥100 IU/mL and < 5000 IU/mL
- ALT ≤ 2 × ULN
- Non-cirrhotic

Protocol decision rules:

- Optional 2nd MVA-HBV boost/placebo dose at Week 38:
  - Additional ≥0.5 $\log_{10}$ HBsAg decline between Weeks 26 and 34
- **NA discontinuation occurred after Week 48/EOT visit if all criteria were met:**
  - HBV DNA < LLOQ
  - HBeAg negative
  - HBsAg < 100 IU/mL
  - ALT <2 × ULN

*Data cut date April 12, 2024

Demographics: Baseline characteristics were comparable between groups

- Median baseline HBsAg was over 800 IU/mL in each Group
- Mostly male, Asian, with HBV genotype B or C
- More HBeAg+ subjects were randomized to Group B/placebo (not stratified)

Parameter	Group A VTP-300 (N=20)	Group B Placebo (N=20)	Total (N=40)
Age, mean (SD)	52.2 (6.45)	44.3 (8.33)	48.2 (8.37)
Males, n (%)	14 (70)	14 (70)	28 (70.0)
Race			
Asian	18 (90)	19 (95)	37 (92.5)
White	1 (5)	1 (5)	2 (5.0)
Black/African American	1 (5)	0	1 (2.5)
HBV Genotype, n (%)			
B	5 (25)	7 (35)	12 (30)
C	7 (35)	7 (35)	14 (35)
D	1 (5)	0	1 (2.5)
Not detected*	7 (35)	6 (30)	13 (32.5)
HBsAg, IU/mL			
Median	820	870	820
Mean	1123	1135	1129
Range	95 - 4000	100 – 3300	95 - 4000
Baseline ALT mean (SD), U/L	20.7 (9.50)	22.1 (11.12)	21.7 (10.23)
HBeAg			
Positive, n (%)	4 (20)	10 (50)	14 (35)
Median (range) (PEI U/mL)	0.19 (0.1 – 89.3)	0.31 (0.1 – 93.1)	0.31 (0.1 – 93.1)

*Subjects were NA suppressed at baseline, thus not all had amplifiable DNA or RNA for sequencing

Assay methods:

Parameter	Assay Method	Lower Limit of Quantitation	Imputed values for results <LLOQ
HBsAg	Diasorin Liaison XL	0.05 IU/mL	0.035 IU/mL
HBV DNA	Cepheid GeneXpert	10 IU/mL	<LLOQ = 5, TND = 1
HBeAg	Diasorin Liaison XL	0.09 PEI U/mL	0.055 PEI U/mL
HBsAb	Siemens Centaur	10 mIU/mL	3.1 mIU/mL
HBV pgRNA	Abbott HBV pgRNA V2.0 (RUO)	0.49 log U/mL	0.48 log U/mL
HBcrAg	Fujirebio Lumipulse G	3 log U/mL	1.45 log U/mL
HBV GT	DNA/RNA Sequencing	Not amplifiable	N/A

Safety: The combination of imdusiran and VTP-300 was well-tolerated

Subjects, N (%) [Events]	Imdusiran Lead-in (N=40)	Group A VTP-300 (N=20)	Group B Placebo (N=20)	Study Total (N=40)
Any TEAE	22 (55%) [44]	12 (60%) [22]	12 (60%) [24]	30 (75%) [90]
Grade 1	19 (47.5%) [40]	7 (36.8%) [16]	5 (27.8%) [12]	22 (55.0%) [68]
Grade 2	2 (5.0%) [2]	3 (15.8%) [4]	1 (5.6%) [2]	6 (15.0%) [8]
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Treatment-related TEAEs				
Imdusiran	4 (10%) [8]	1 (5%) [1]	0	5 (12.5%) [9]
VTP-300	N/A	4 (20%) [6]	N/A	4 (10%) [6]
SAEs	0	0	0	0
Treatment discontinuation	0	0	0	0

TEAE: treatment-emergent adverse event; SAE: serious adverse event

- Most common treatment-related TEAEs in 2 or more subjects (all Grade 1 or 2):
  - Imdusiran: injection site-related (bruising and/or swelling in 2 subjects), ALT increased in 2 subjects
  - VTP-300: injection site-related (redness, pain and/or injection reaction in 2 subjects)
- Only 3 Grade 3 or 4 laboratory abnormalities were observed, none assessed as AEs:
  - Isolated, transient creatine kinase (CK), glucose, and INR elevations in 3 different subjects
- Well-tolerated profiles of imdusiran and VTP-300 were maintained when administered sequentially

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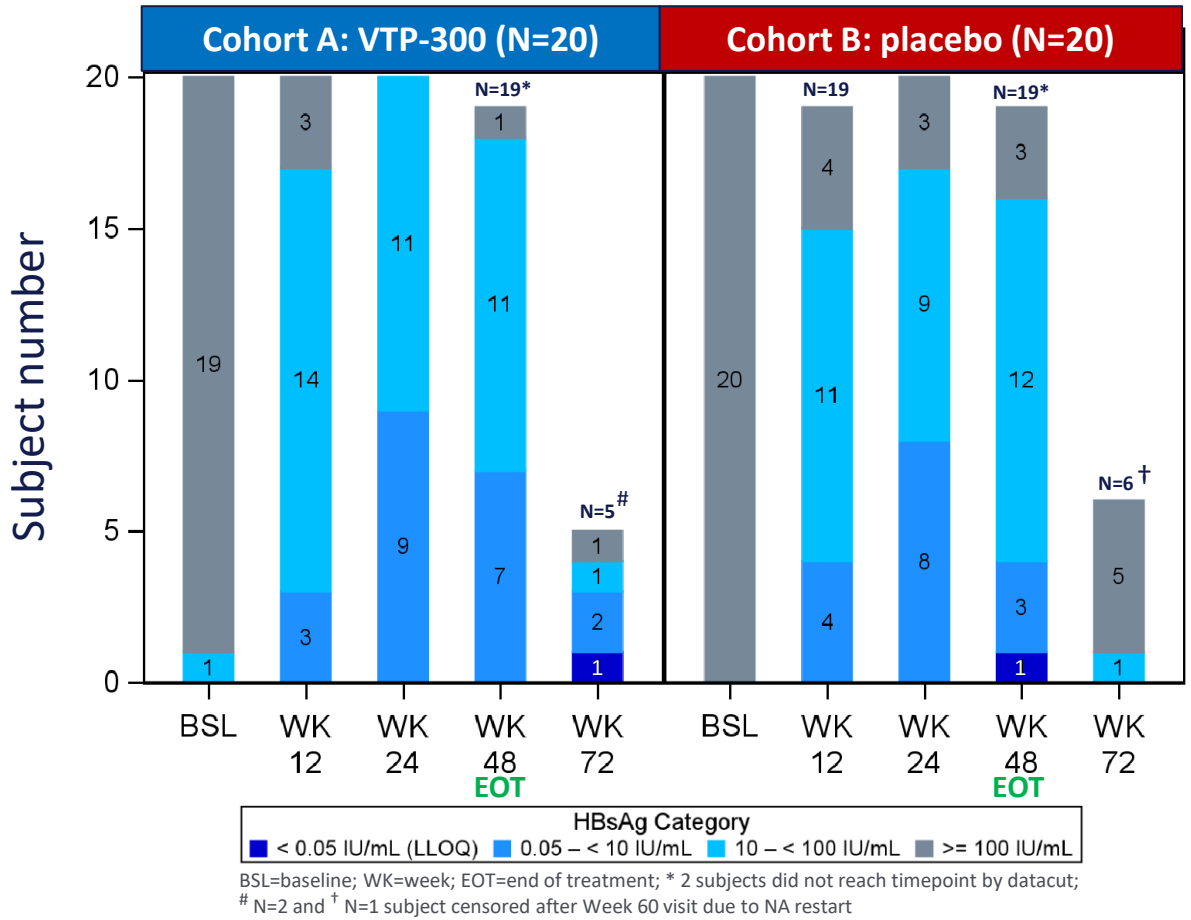
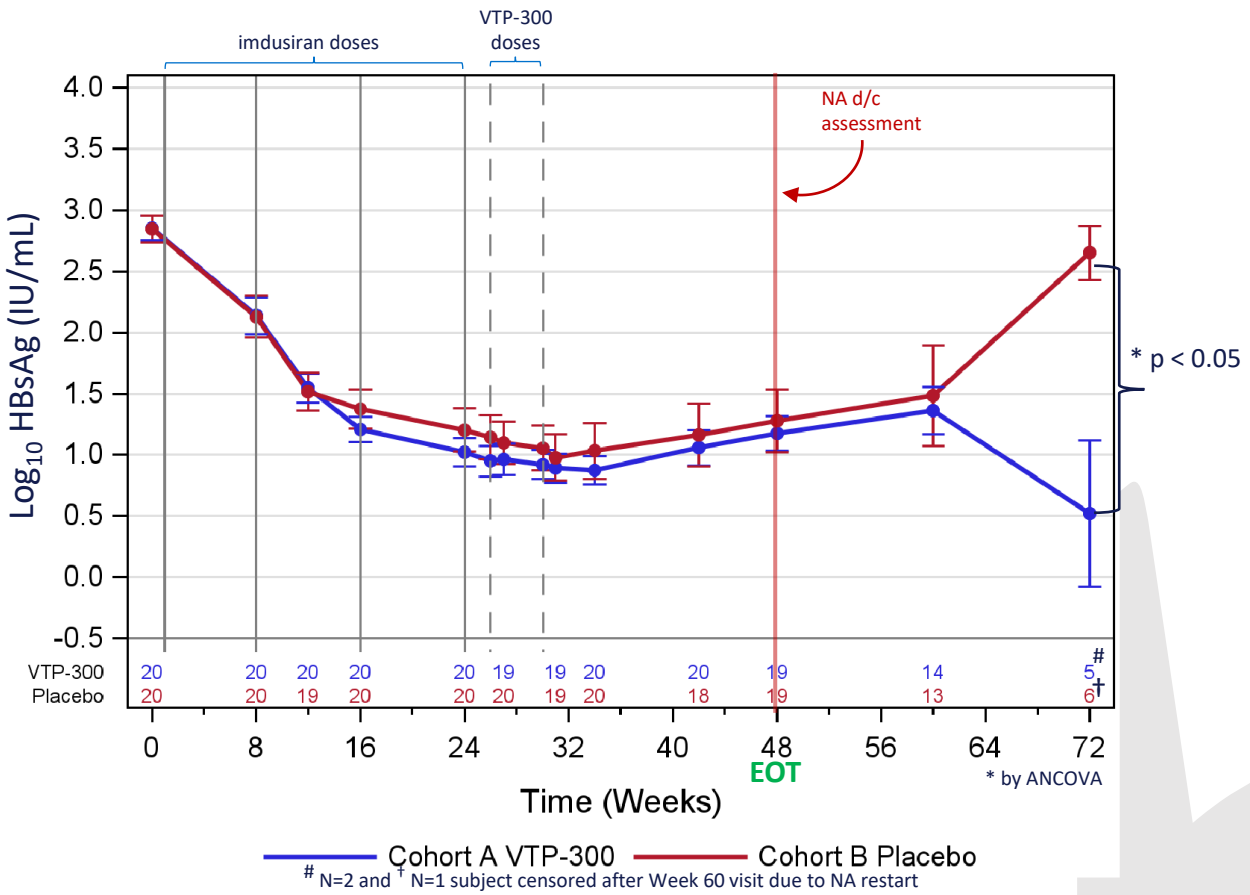
Results: Lower HBsAg levels maintained over time in VTP-300 group

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

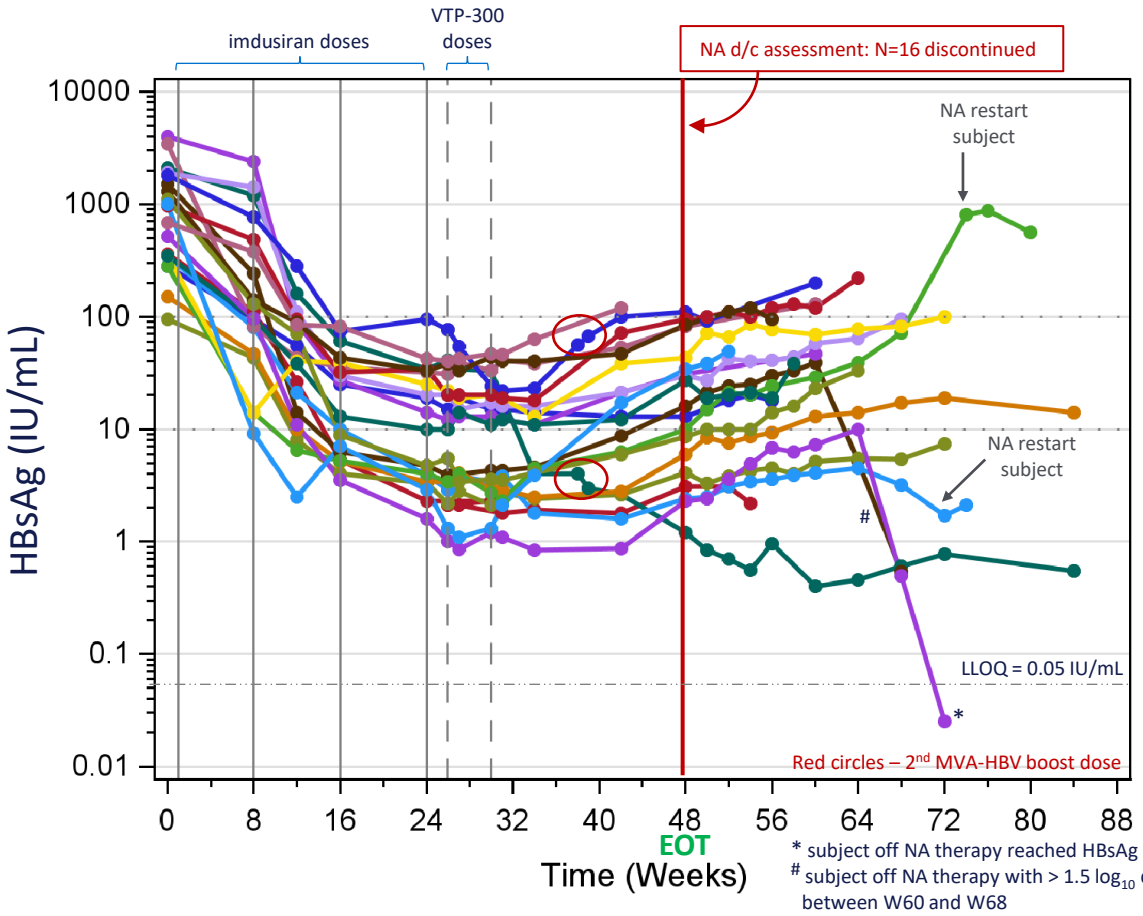


N=2 and † N=1 subject censored after Week 60 visit due to NA restart

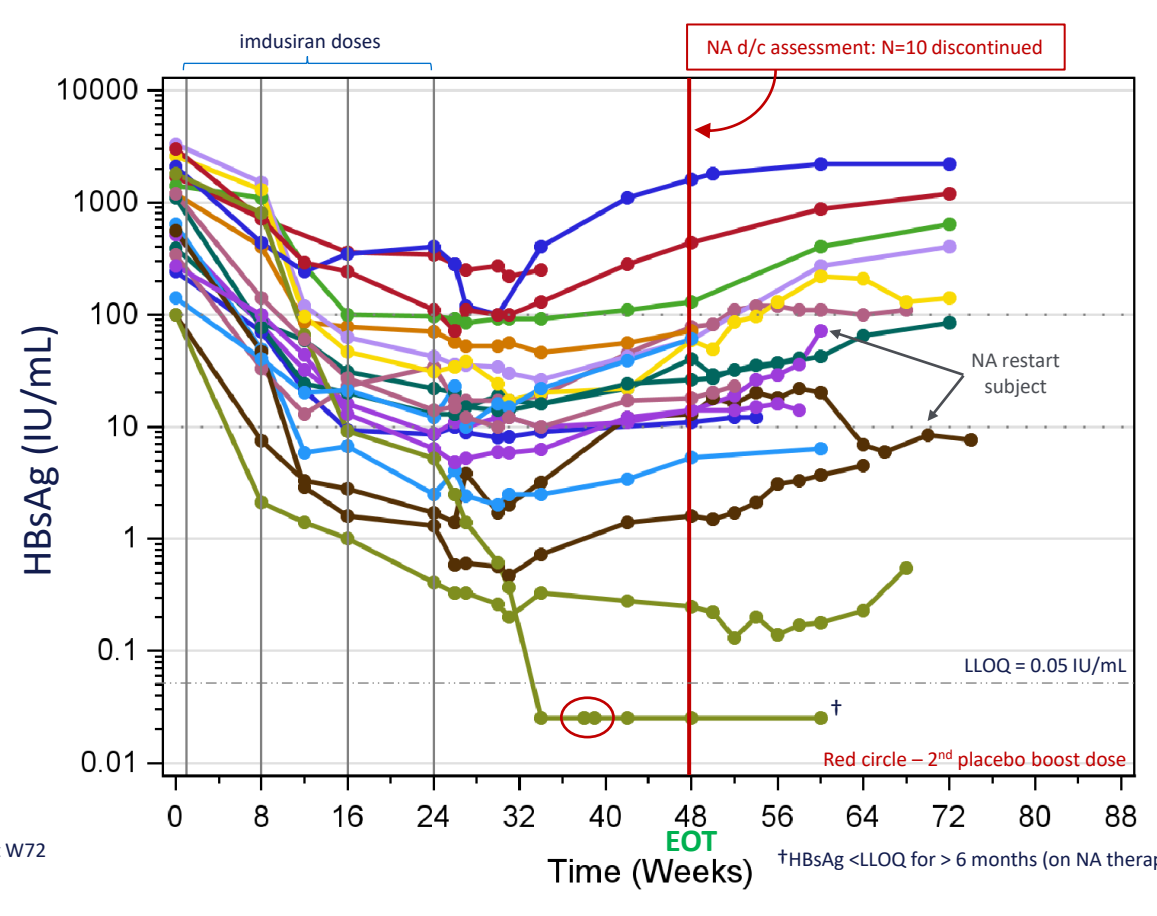
- Imdusiran led to declines of -1.8 log_{10} by Week 26, 95% of subjects had HBsAg <100 at time of VTP-300 or placebo dosing
- More subjects maintained HBsAg thresholds of <100 IU/mL and <10 IU/mL when administered VTP-300 vs placebo
- At 24 weeks post-EOT (Week 72, N=11), there was a significant difference in HBsAg levels between groups, which may reflect the delayed effect of VTP-300 on HBsAg levels observed in other trials

Results: Individual Subject HBsAg Declines by Treatment Group

Group A (VTP-300) Individual Subject HBsAg Declines



Group B (placebo) Individual Subject HBsAg Declines



- More subjects in Group A/VTP-300 have maintained low HBsAg levels at and after end of treatment
  - 1 Group A/VTP-300 subject off NA therapy [*] reached HBsAg <LLOQ at Week 72 after >2 $\log_{10}$ decline between Week 64 and 72, another subject off NA therapy [#] has had >1.5 $\log_{10}$ decline in HBsAg between Week 60 and 68
  - 1 subject in Group B/placebo has had continuous HBsAg <LLOQ for > 6 months (remained on NA therapy due to positive HBeAg status at Week 48)

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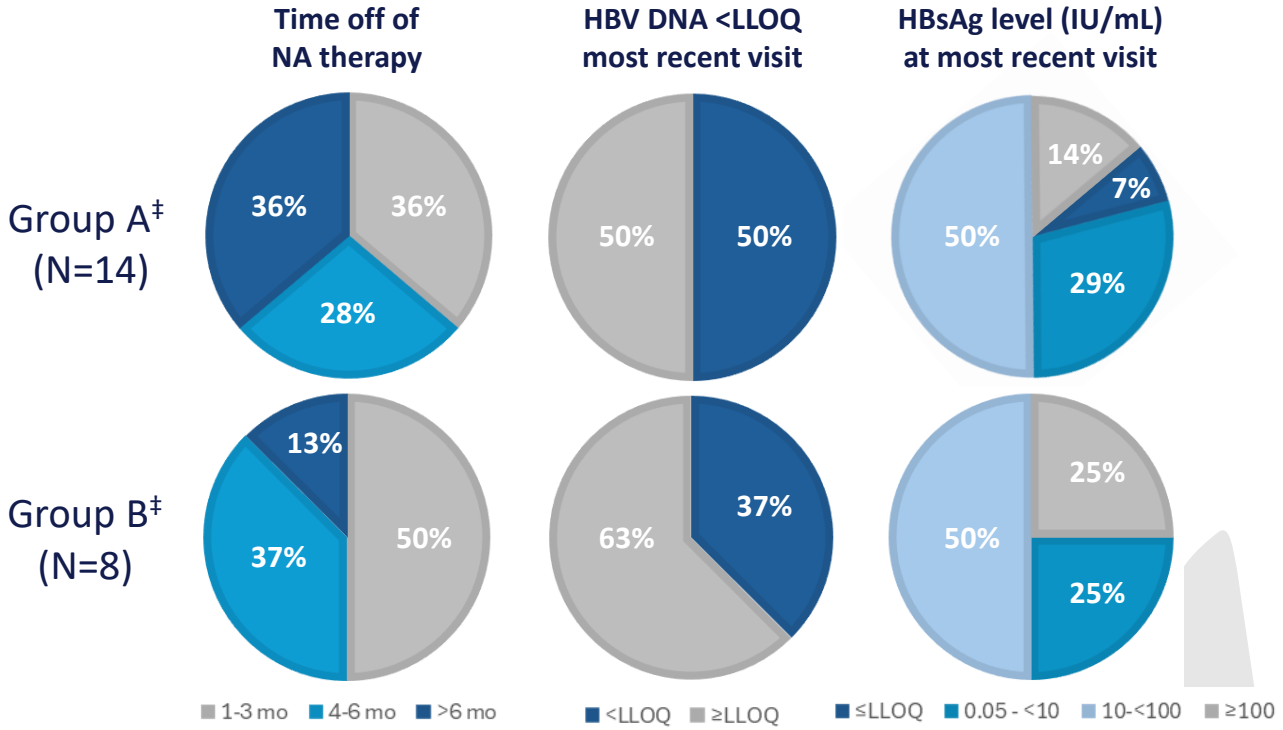
Results: More subjects in Group A/VTP-300 stopped NA treatment

NA Discontinuation Summary N, (%)	Group A VTP-300	Group B placebo
Stopped NA treatment after Week 48[#] (HBV DNA <LLOQ, HBeAg-, ALT <2x ULN, HBsAg <100 IU/mL)	16/19 (84%)	10/19 (53%)
Did not meet NA stopping criteria:	3/19 (16%)	9/19 (47%)
HBeAg+	2/3	9/9*
HBsAg > 100 IU/mL	1/3	3/9*
Met NA restart criteria[†]	2/16 (13%)	2/10 (20%)

[#] 2 subjects (1 in each Group) had not reached Week 48 timepoint as of data cut date

* 3 subjects were both HBeAg+ and had HBsAg >100 IU/mL

[†] All NA restarts were due to confirmed HBV DNA >20,000 IU/mL **without** ALT >2x ULN



‡ only subjects who remained off NA therapy included

- More subjects in Group A/VTP-300 met NA discontinuation criteria and stopped treatment
  - More Group A/VTP-300 subjects (50%) have maintained HBV DNA <LLOQ off NA therapy than placebo subjects (37.5%)
  - Group A/VTP-300 subjects have maintained lower HBsAg levels after NA discontinuation
    - 1 Group A/VTP-300 subject reached HBsAg <LLOQ at Week 72, another has >1.5 $\log_{10}$ HBsAg decline between Week 60 and 68
- NA discontinuation was well-tolerated with frequent follow-up visits and testing of HBV DNA and clinical safety labs
  - Maximal ALT of 80 U/L prior to NA restart amongst 4 subjects who restarted treatment
  - 1 subject had isolated, transient ALT of 156 U/mL after single HBV DNA elevation that spontaneously resolved without re-treatment, subsequently led to HBsAg <LLOQ

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Conclusions

- Imdusiran 60 mg every 8 weeks for 24 weeks followed by VTP-300 or placebo was well-tolerated
- The combination of imdusiran and VTP-300 led to maintenance of lower HBsAg levels during the post-treatment follow-up period
- Nucleos(t)ide analogue discontinuation was achieved in the majority of subjects, with more meeting the discontinuation criteria in the VTP-300 group (84%) vs placebo (53%)
  - More subjects in the VTP-300 group have maintained HBV DNA < LLOQ and lower HBsAg levels off NA treatment vs placebo
  - NA discontinuation was well-tolerated, including in the 4 subjects who restarted NA therapy due to HBV DNA increases
  - No concerning ALT elevations were observed in those subjects
- Two VTP-300 subjects have had significant (>1.5 $\log_{10}$) HBsAg declines in the early NA discontinuation follow-up period with one subject reaching HBsAg <LLOQ, suggesting a delayed effect of VTP-300 on HBsAg levels as has been previously observed

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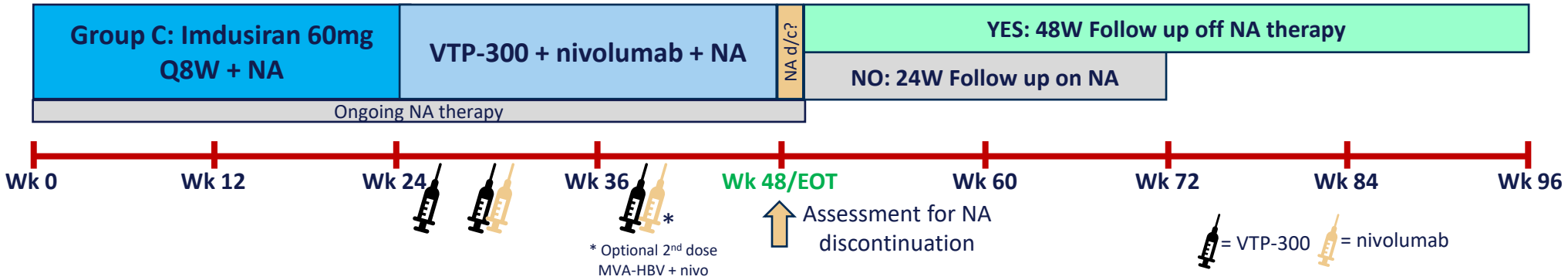
Additional imdusiran and VTP-300 data:

- Please see Abstract #2823 (Poster WED-375): Yuen, MF et al., VTP-300 immunotherapeutic, plus low dose PD-1 inhibitor, nivolumab, continues to show meaningful, sustained reductions in HBsAg levels
- The IM-PROVE II (AB-729-202) low dose nivolumab arm (Group C) is fully enrolled, end of treatment data is expected 2H2024



Acknowledgements

Arbutus Biopharma and Barinthus Biotherapeutics thank all participating subjects and their families, the Investigators and site staff, Novotech CRO, Eurofins, Maksym Chernyakhovskyy (Arbutus) and Crystal Grant (Arbutus) for data management assistance, Deepa Patel (Arbutus) and Dereck Tait (Barinthus) for study support, and the imdusiran and VTP-300 Research and Development Teams.

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