Evidence of T Cell Restoration after siRNA Therapy

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NASDAQ: ABUS

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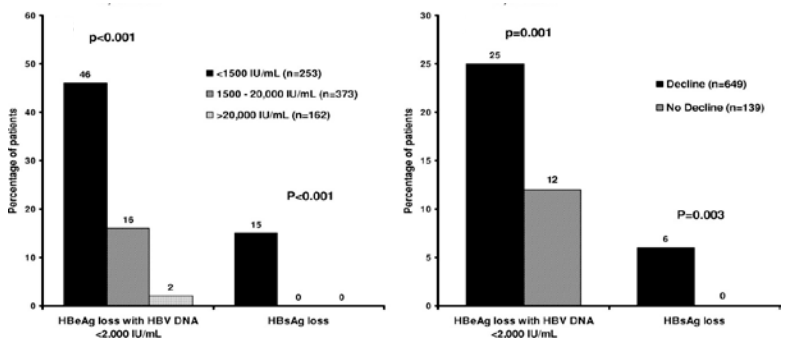
Disclosure Statement

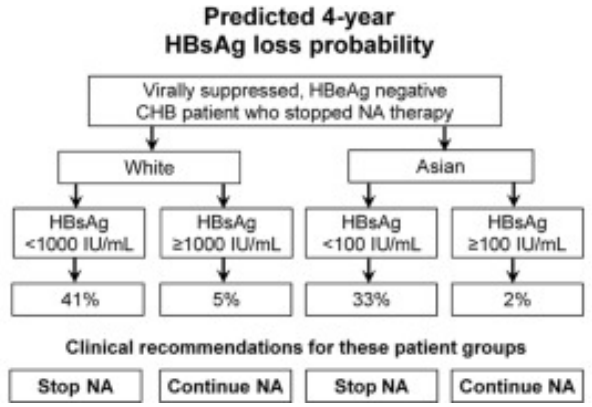
The authors affiliated with Arbutus Biopharma are current and former employees and may hold company stock.

Rationale: HBsAg and Treatment Response

- Low baseline and rapid change in HBsAg levels has been associated with better responses in patients treated with:
  - pegIFN-α
  - Nucleo(s)tide analogues (NA)
  - Checkpoint inhibitors
  - Therapeutic vaccines
- Low HBsAg and/or undetectable HBcrAg at end of treatment has been associated with a greater probability of HBsAg loss in patients after NA withdrawal
- Age but not HBsAg has been observed to correlate with peripheral HBV-specific T cell responsiveness in naïve and TDF-treated patients
  - ➢ Rapid declines in HBsAg and other antigens mediated by RNAi may elicit responses that are distinct from naturally low HBsAg



Sonneveld et al., Hepatol., 2013



Hirode et al., Gastroenterol., 2022

Wang et al., AASLD 2021
Evans et al., EASL 2022
Papatheodoridi et al., J Viral Hepat., 2020
Sonneveld et al., J Hepatol., 2022
Terrault et al., Hepatol., 2021
Le Bert et al., Gastroenterol., 2020

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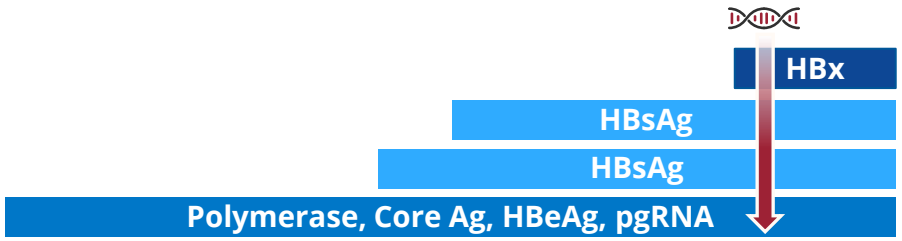
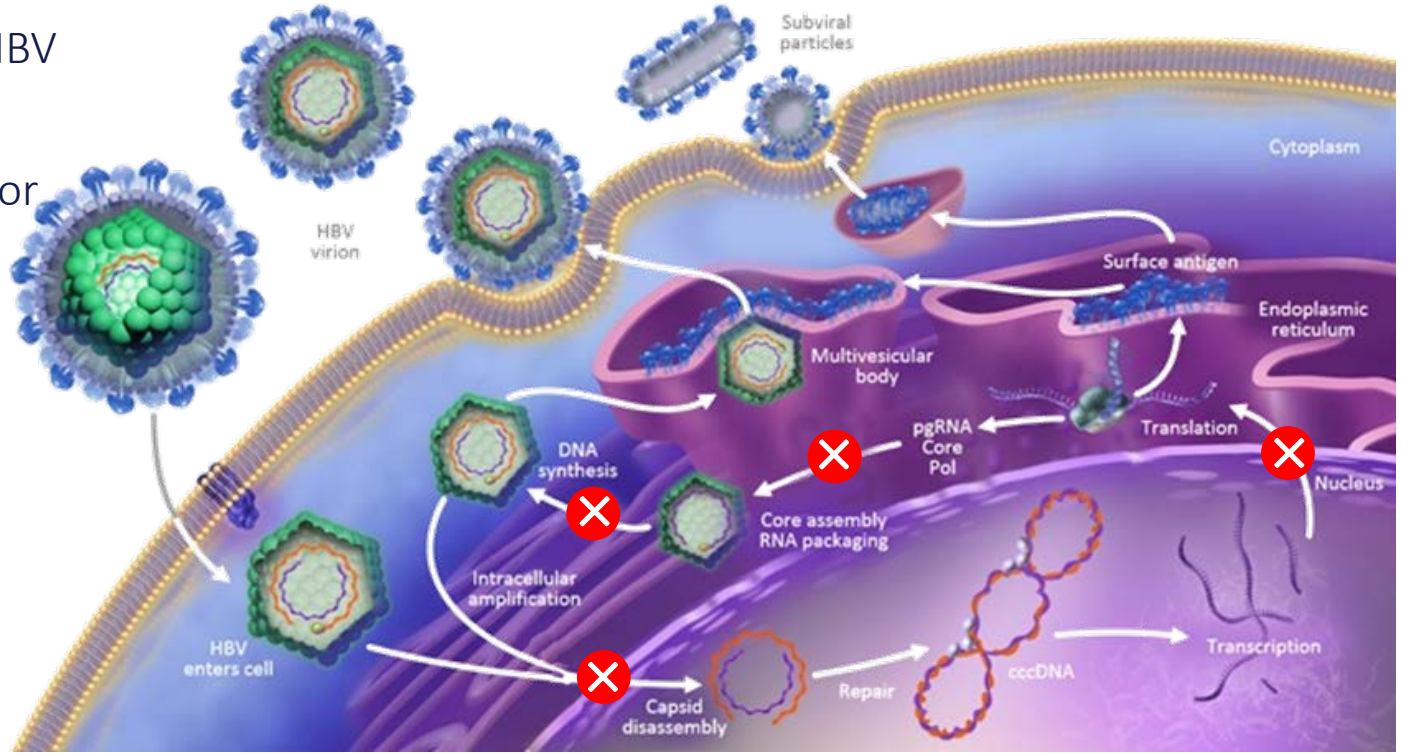
AB-729, an RNAi Therapeutic for CHB

- AB-729 is a subcutaneously administered single trigger GalNAc-conjugated siRNA therapeutic candidate
- Targets all HBV RNA leading to reduction of HBV antigens including HBsAg
- AB-729 is currently in Phase 2 development for the treatment of CHB in combination with other agents





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AB-729-001

- 3-part study examining safety and pharmacodynamics of single and repeat doses of AB-729 in healthy subjects and CHB subjects
- Subjects in Part 3 were dosed with AB-729 for 24 weeks + optional extension to continue through Wk 48
- NA discontinuation eligibility was determined using the following criteria at least 24 wks post-last dose of AB-729:
  - ALT <2 × ULN, and
  - Undetectable (target not detected) HBV DNA, and
  - HBeAg negative, and
  - HBsAg <100 IU/mL at two consecutive visits

Part 3: Multiple Doses In Chronic Hepatitis B Subjects

- Cohort E: 60 mg Q4W HBV DNA - n=7
- Cohort F: 60 mg Q8W HBV DNA - n=7
- Cohort G: 90 mg Q8W +TDF HBV DNA + n=7
- Cohort I: 90 mg Q8W HBV DNA - n=6
- Cohort J: 90 mg Q12W HBV DNA - n=7
- Cohort K: 90 mg Q8W HBV DNA -, HBeAg+ n=7

Baseline Measure[#]	HBV DNA-	
	Cohort E[‡] (N=7)	Cohort F (N=7)
Age in years, mean (range)	45.1 (33 – 63)	44.0 (31 – 59)
Male gender, n (%)	4 (57)	4 (57)
BMI, mean (SD)	27.7 (5.0)	23.7 (2.2)
Race, n (%)		
Asian	1 (14)	5 (71)
Black	0	1 (14)
White	6 (86)	1 (14)
Pacific Islander	0	0
ALT (U/L), mean (SD)	22.4 (10.5)	23.4 (15.2)
HBV eAg negative, n (%)	7 (100)	6 (71)[◊]
HBsAg (IU/mL), mean (range)	5,372 (584 – 11,761)	5,354 (667 – 18,605)

[#] Genotype not determined
‡ Subjects switched to AB-729 60 mg Q12W for the extension phase
[◊] One subject counted as HBeAg negative was identified as "HBeAg borderline" (baseline HBeAg = 0.18 IU/mL, LLOQ = 0.11 IU/mL)

Longitudinal PBMC samples collected in a subset of subjects (N = 7) for HBV-specific T cell IFN-γ fluorospot, T cell proliferation assays and immunophenotyping

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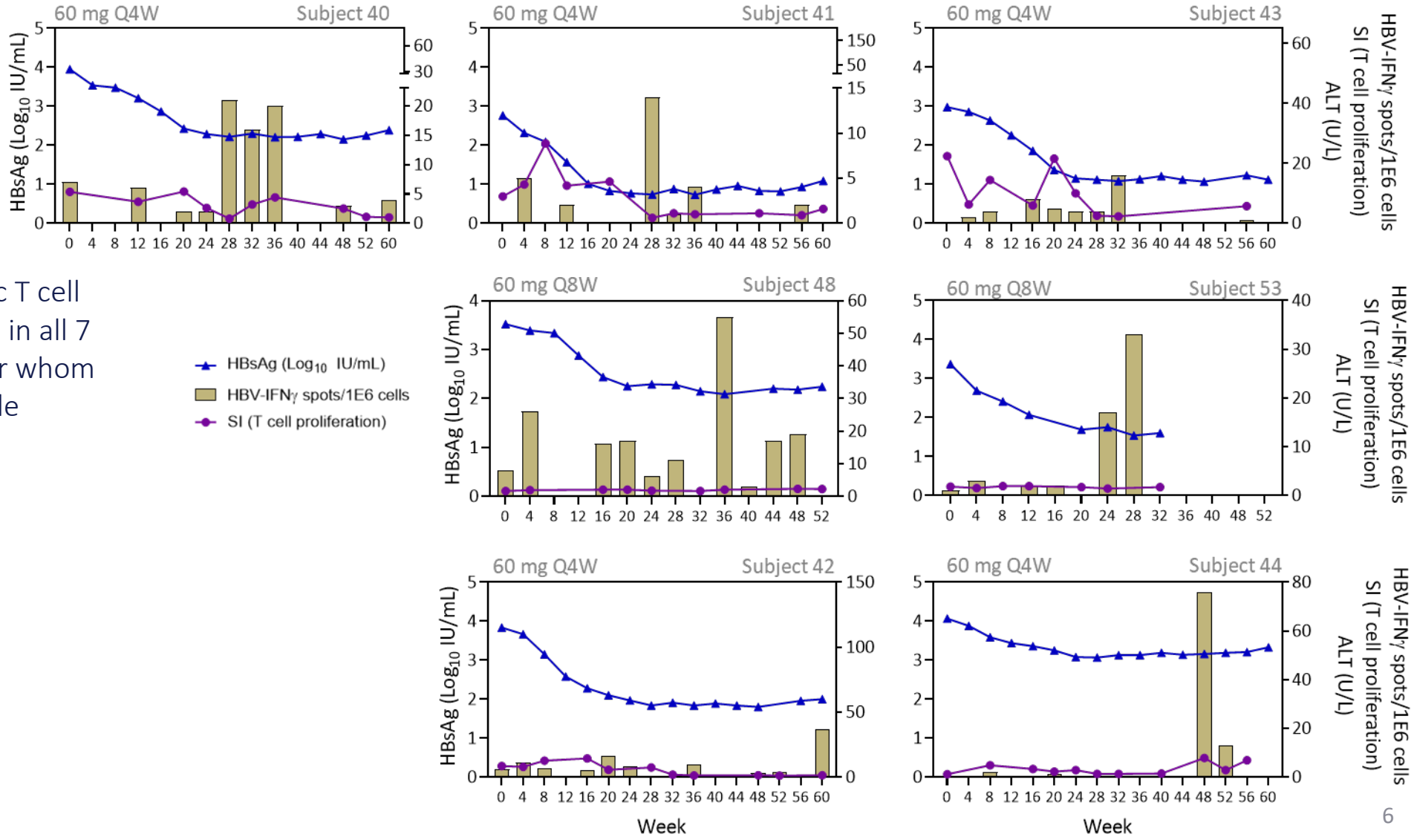
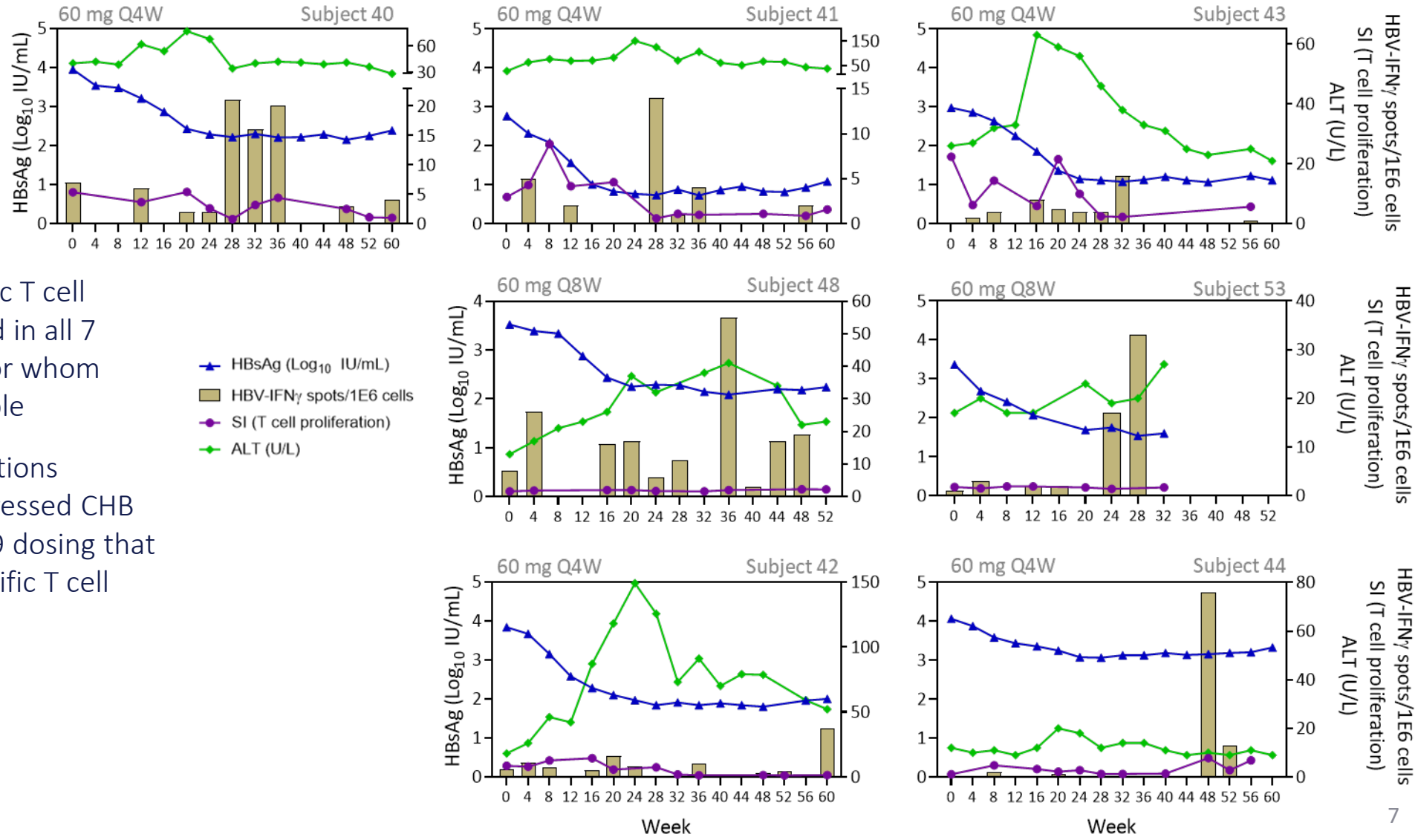
HBV-Specific T Cell Activation Markers are Upregulated in CHB Subjects Undergoing AB-729 Dosing

- Upregulation of HBV-specific T cell activation markers observed in all 7 subjects assessed to date for whom PBMC samples were available



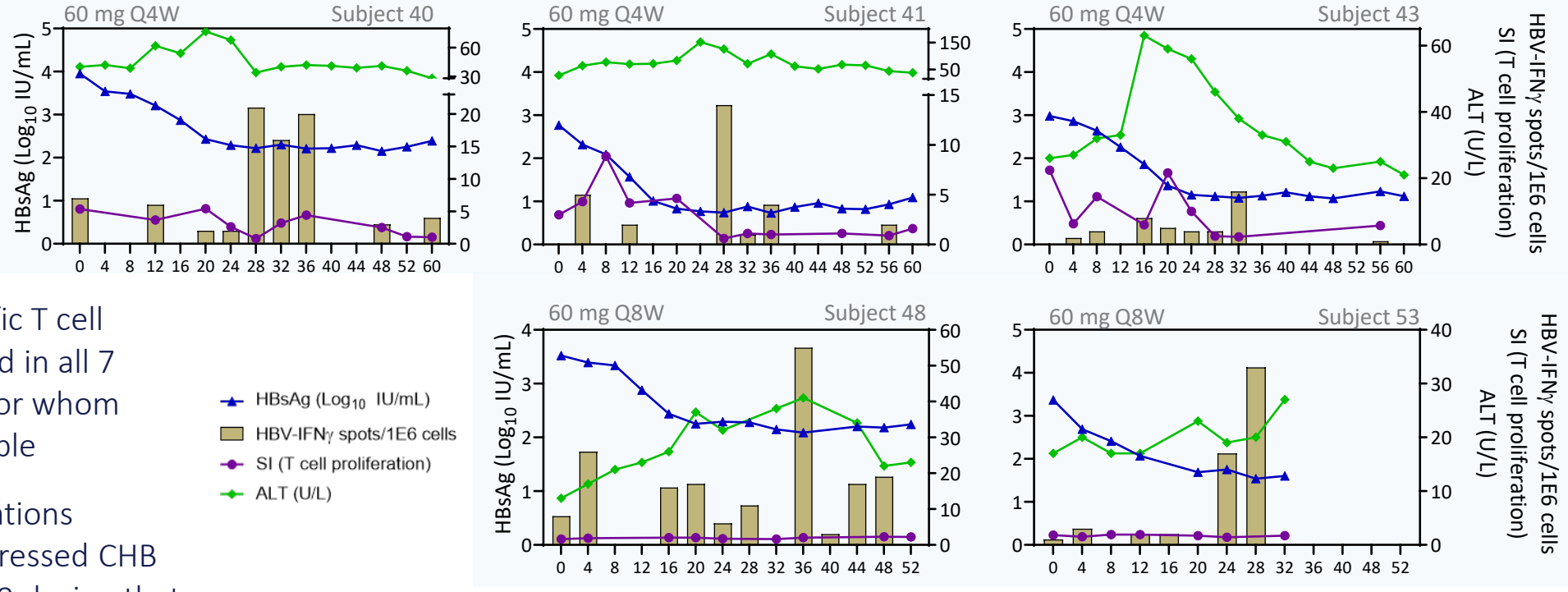
HBV-Specific T Cell Activation Markers are Upregulated in CHB Subjects Undergoing AB-729 Dosing

- Upregulation of HBV-specific T cell activation markers observed in all 7 subjects assessed to date for whom PBMC samples were available
- Mild to moderate ALT elevations observed in some NA-suppressed CHB subjects undergoing AB-729 dosing that is associated with HBV-specific T cell IFN-γ production



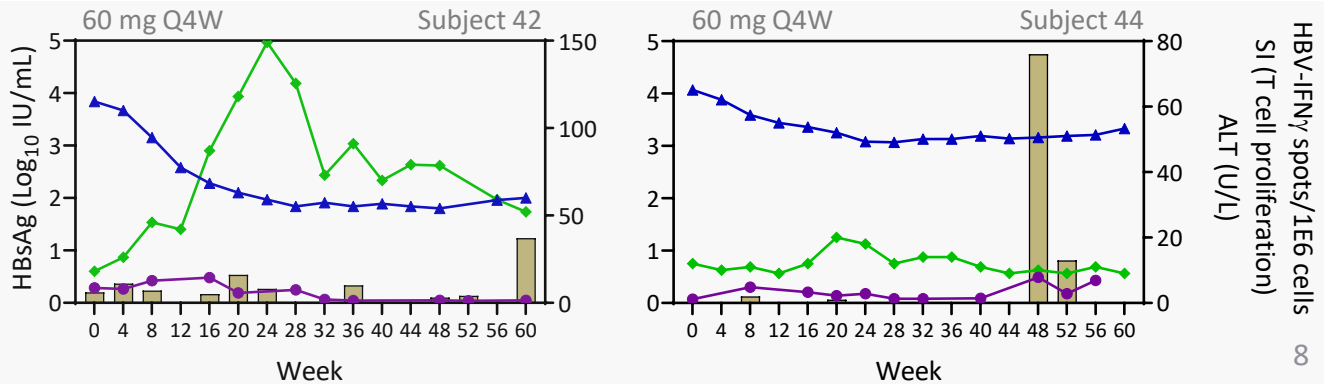
HBV-Specific T Cell Activation Markers are Upregulated in CHB Subjects Undergoing AB-729 Dosing

Elevation **during AB-729** dosing



- Upregulation of HBV-specific T cell activation markers observed in all 7 subjects assessed to date for whom PBMC samples were available
- Mild to moderate ALT elevations observed in some NA-suppressed CHB subjects undergoing AB-729 dosing that is associated with HBV-specific T cell IFN-γ production
- Two profiles of HBV-specific T cell IFN-γ responses observed

Elevation **after AB-729** dosing



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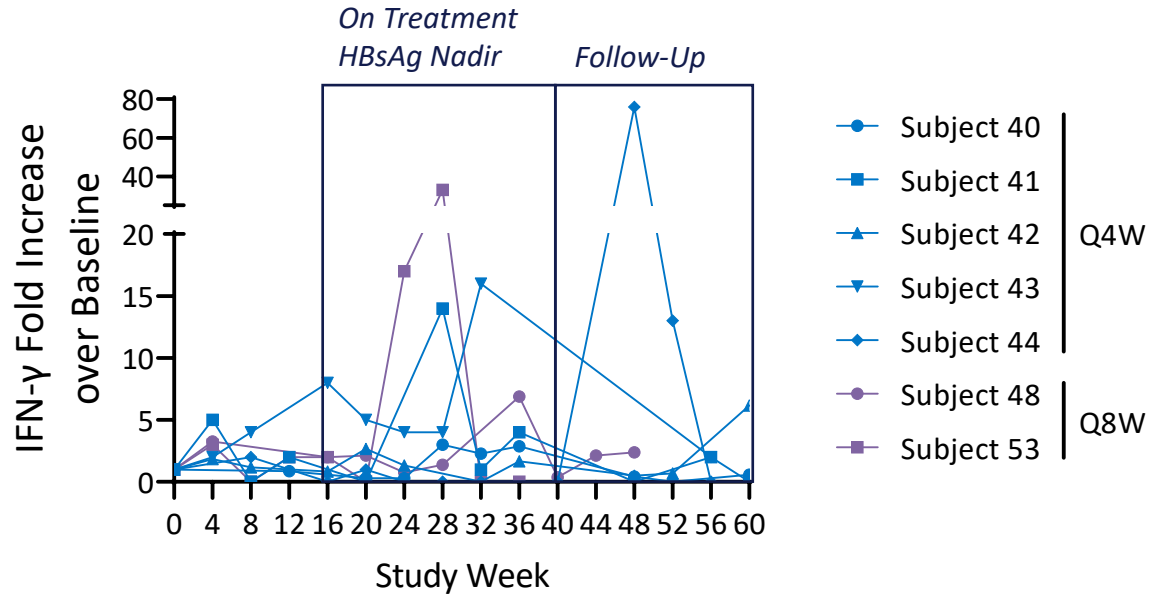
HBV-Specific T Cell Activation Markers are Upregulated in CHB Subjects Undergoing AB-729 Dosing

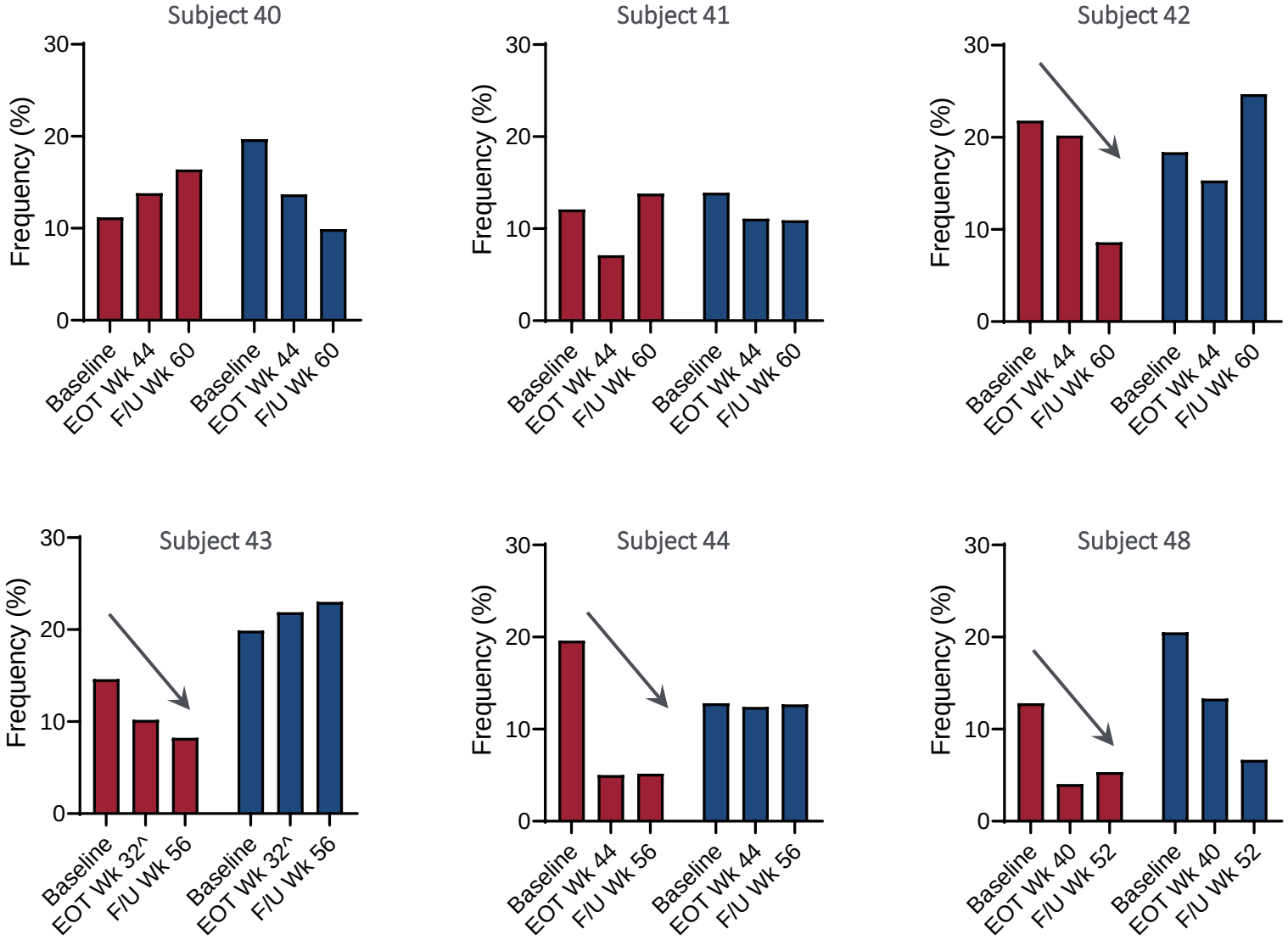


- Two profiles of HBV-specific T cell IFN-γ responses observed
  - Elevation **during AB-729** dosing, which coincides with nadir of HBsAg reduction
  - Elevation **after AB-729** dosing completed, between Week 48-60

Subjects assessed to date for whom PBMC samples were available

Decline of CD8+ Exhausted T Cells in CHB Subjects Undergoing AB-729 Dosing

- In 4 out of 6 subjects, frequency of exhausted CD8+ T cells declined at EOT and persisted up to 12-16 wks after last dose of AB-729
- No obvious trend was seen with exhausted or effector CD4+ T cells



Exhausted CD8+ T cells = CD8+ CD45RA- PD-1+ Tox+ Bcl2-
Effector CD8+ T cells = CD8+ CD45RA- PD-1+ Tox- Bcl2+

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

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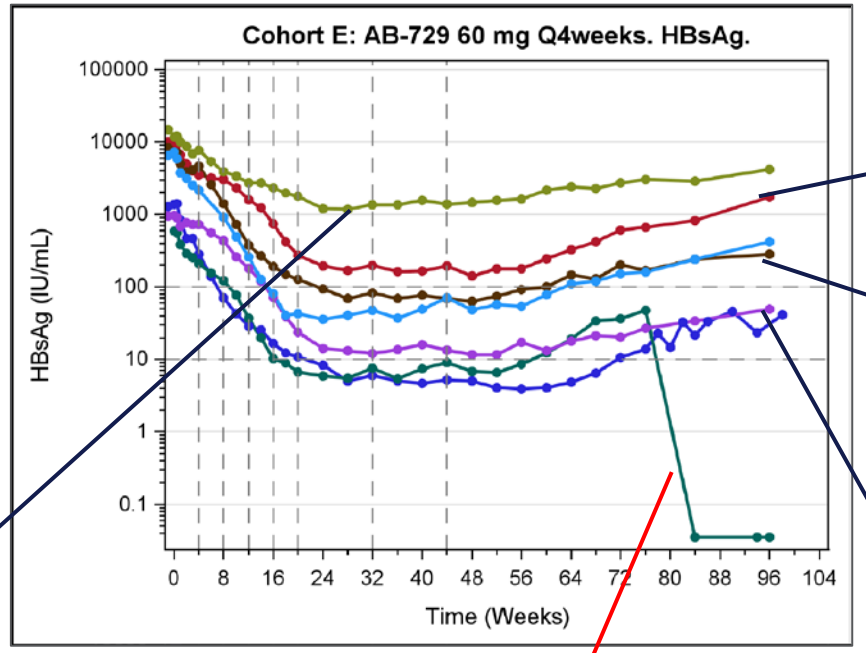
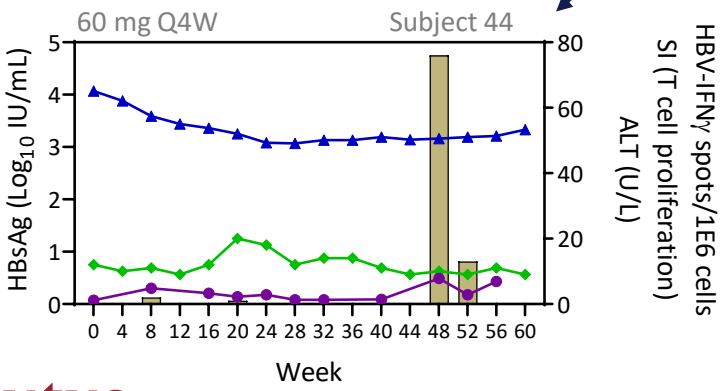
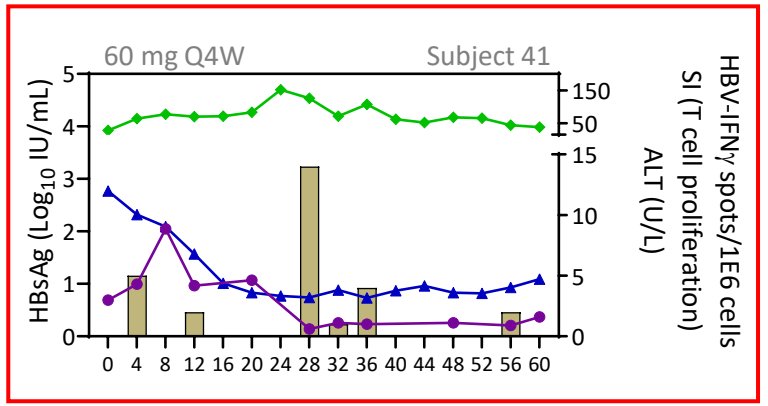
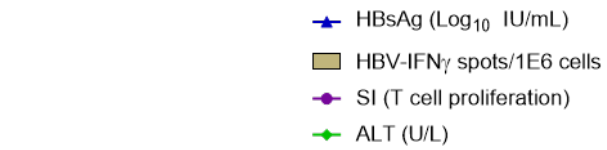
Association with Clinical Outcomes

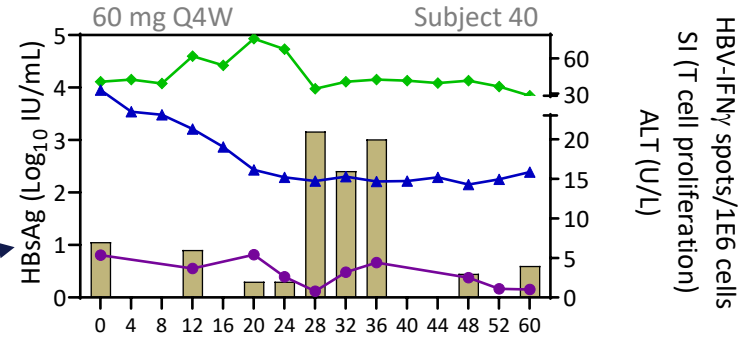
- Subject 41 seroconverted and HBsAg became <LLOQ at Wk 84, 40 wks after last dose of AB-729 (beyond current T cell data set)
  - Subject remained on NA after stopping AB-729
- Remaining 4 subjects did not meet pre-defined NA discontinuation criteria

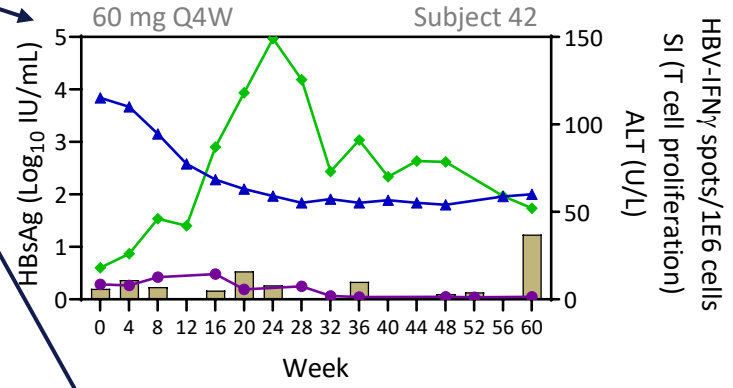


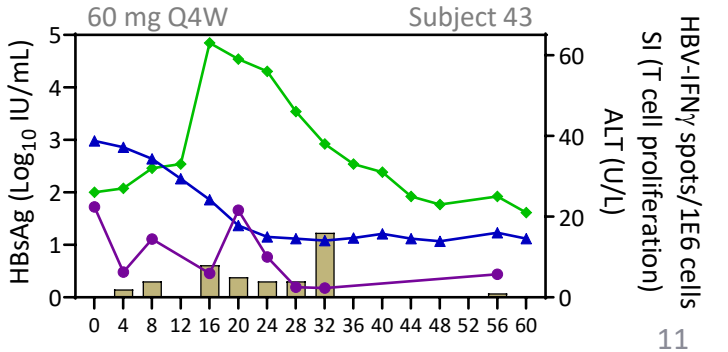






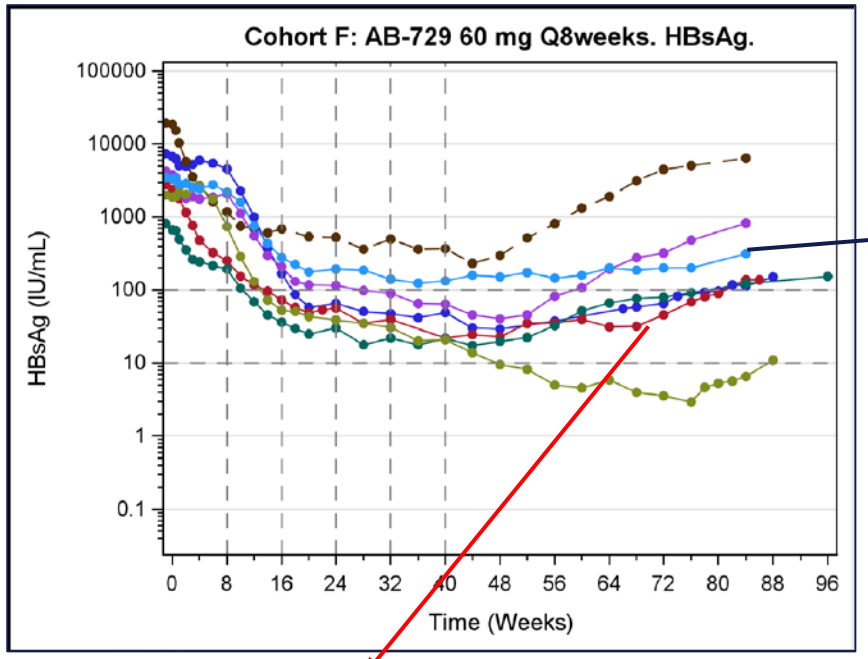


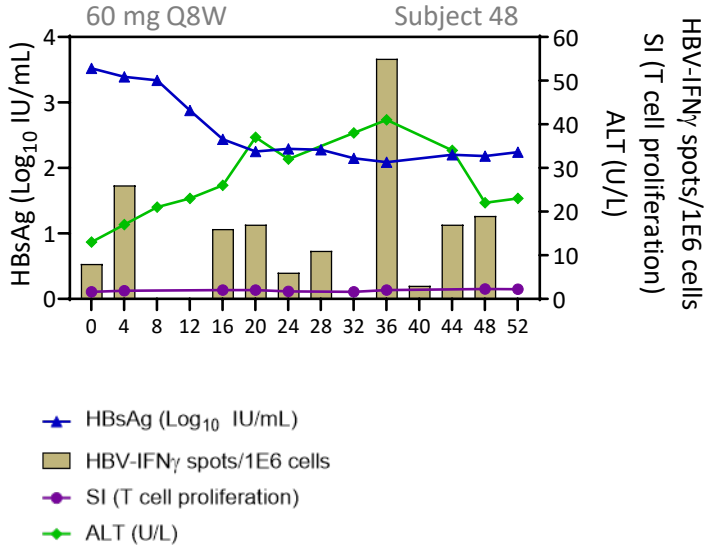


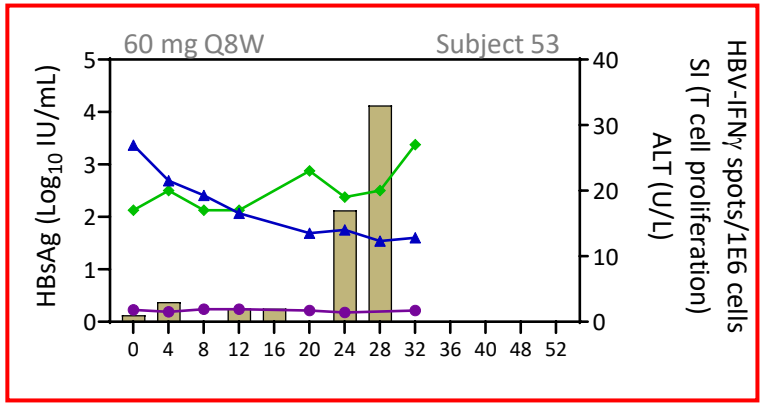


Association with Clinical Outcomes

- Subject 53 met pre-defined NA discontinuation criteria and elected to stop NA treatment
- Other subject did not meet NA discontinuation criteria







Summary

- AB-729-mediated HBsAg reduction is associated with increased HBV-specific T cell activation and proliferation from baseline in CHB subjects
- A decline in exhausted CD8+ T cells at end of treatment and at 12-16 weeks of follow-up suggests that HBV-specific T cell immune reawakening may be durable
- The limited data thus far suggests that an increase in HBV-specific T cell activation at the nadir of HBsAg reduction may be beneficial to clinical outcomes
    - Profiling greater numbers of subjects with different outcomes is warranted
- Results suggest effects of AB-729 treatment may be enhanced by combination with immunomodulatory agents

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Thank You