A phase 1b evaluation of HepTcell HBV-specific immunotherapy in nuc-controlled, eAg negative chronic HBV infection

Professor Mark Thursz
Imperial College London
for the
Vatic Study Group

Disclosures

Grant Funding

- *Medical Research Council UK*
- *National Institute for Health Research, UK*
- *Novartis*
- *Gilead*
- *GSK*
- *Norgine*

Consultancy / Speaker Fees

- *Altimmune*
- *Affimune*
- *Novartis*
- *Shionogi*

Goal—Functional Cure of HBV

Cellular Immune Responses are Critical to HBV Functional Cure

- Chronic Infection is associated with exhausted T cell phenotype
- Spontaneous Loss of sAg is associated with HBV-specific CD4+ and CD8+ T-cells responses
- Immunosuppression carries risk of sero-reversion and HBV flare in patients with occult infection
- Core and polymerase-specific T cells predict successful treatment discontinuation without flare[1]

Limitations of Other Immunotherapeutic Approaches

- Non-specific immunomodulators (checkpoint inhibitors or TLR agonists) carry risk of off-target effects
- Many Therapeutic Vaccines have failed
  - Limited to or biased towards surface antigen – significant immune tolerance barrier
  - Full length antigens—Drive responses to variable domains
  - Weak immunogens

[1]Rivino et al. J Clin Invest 2018

HepTcell peptide selection process

BIOINFORMATICS

SEQUENCE CONSERVATION / T CELL EPITOPE PREDICTION

INITIAL PBMC SCREENING

IDENTIFICATION OF IMMUNODOMINANT REGIONS

PBMC TESTING

ADDRESS HBV GENOTYPE
PATIENT ETHNICITY

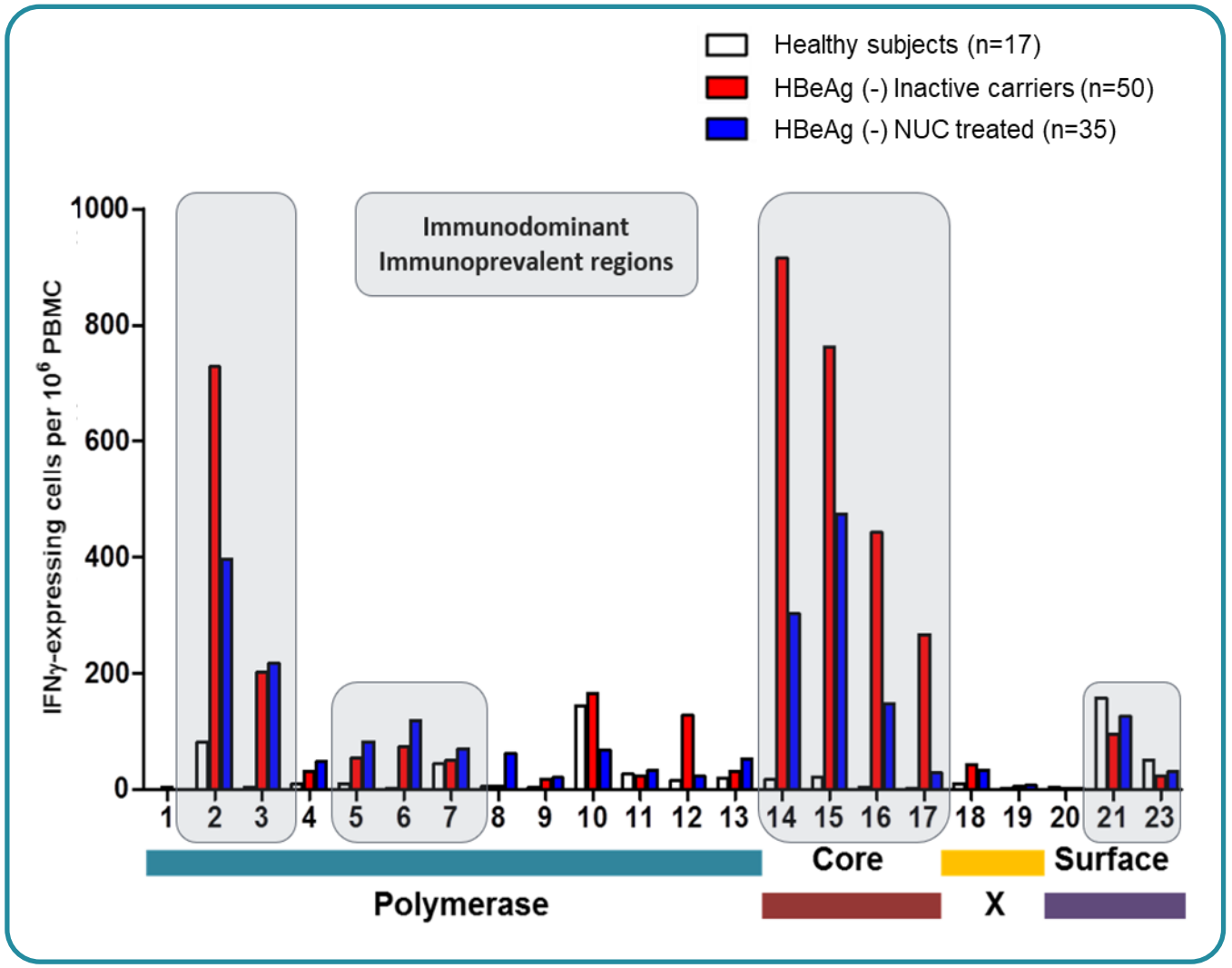
HLA BINDING TESTING

MANUFACTURABILITY

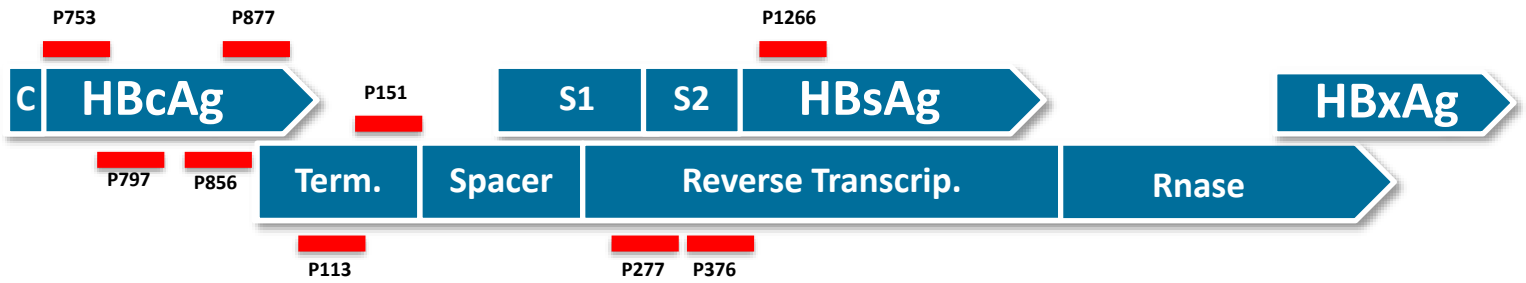
STABILITY

FORMULATION
COMPATIBILITY

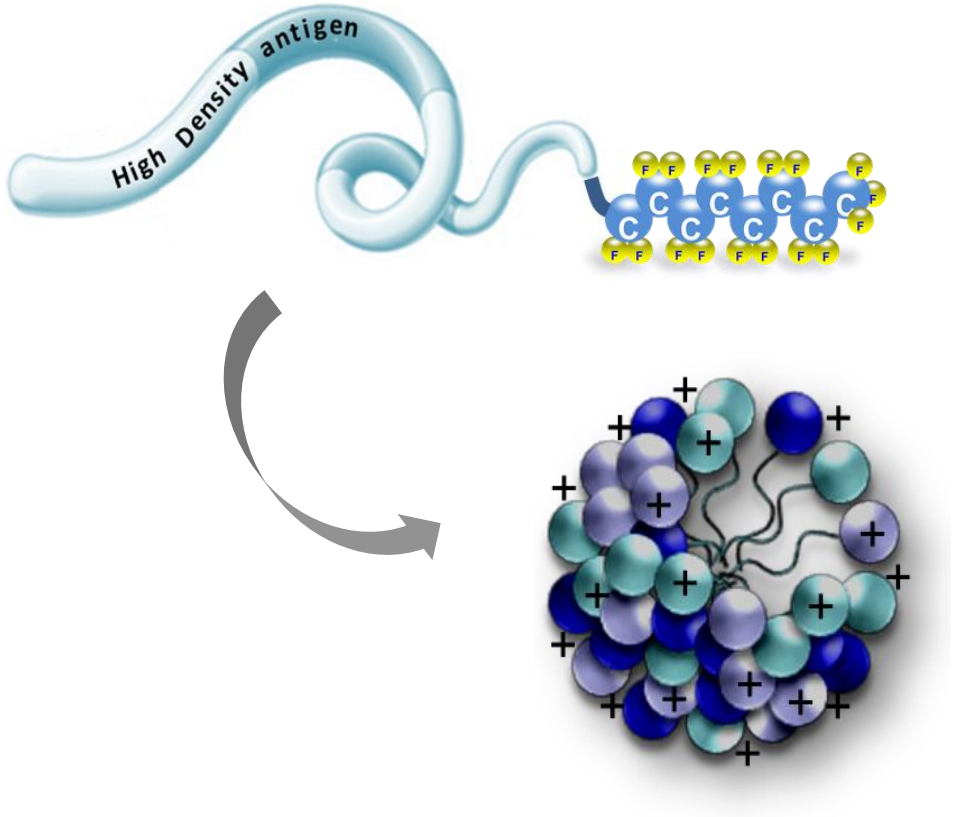
FINAL SELECTION OF 9 LONG PEPTIDES
(EQUIVALENT TO 18% OF HBV PROTEOME)



HepTcell: Fluoropeptide vaccine with depot-forming TLR9 adjuvant



- Nine peptides from highly conserved regions of three different HBV antigens (pol, core and s) common to majority of genotypes
- Demonstrated to stimulate CD4+ and CD8+ T cells in HBV carriers irrespective of HLA background
- Fluorocarbon tail forms immunogenic nanoparticles that resist degradation and enable prolonged immune stimulation
- Similar fluorinated peptide product developed for influenza was safe and immunogenic (>200 exposures)
- IC31® (Valneva) TLR9 adjuvant improved magnitude and breadth of HBV immune response in preclinical models and was associated with excellent tolerability in TB and flu vaccine programs (>650 exposures including infants)



HepTcell Phase 1 Study Design

Population (n=60)

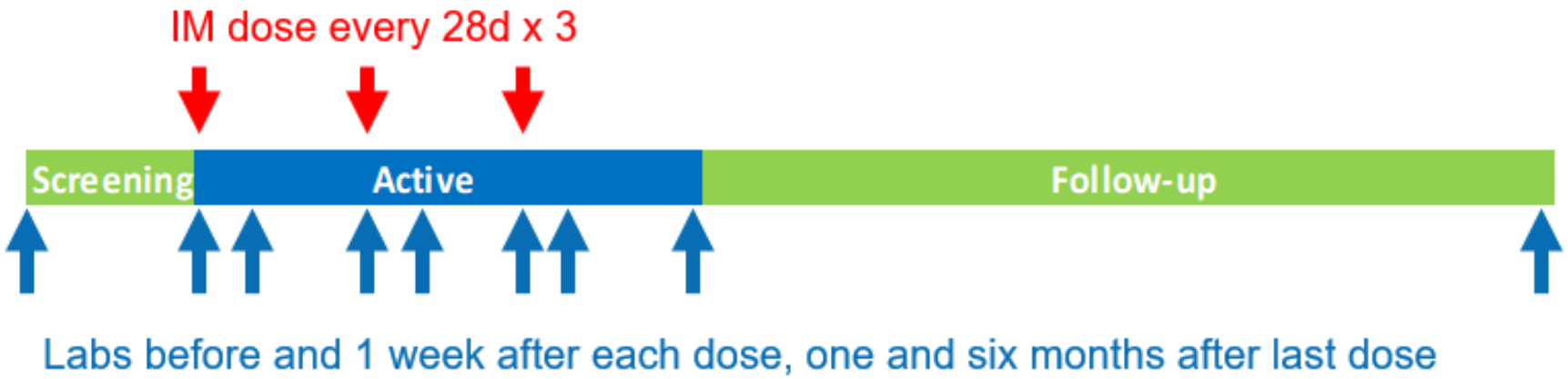
- 18-65 yo with eAg negative chronic HBV for ≥ 2 years
- Tenofovir or entecavir for ≥ 2 years
- HBV DNA <50 IU/ml for ≥ 1year
- No history of cirrhosis and current Fibroscan<11.5 KPa

Endpoints

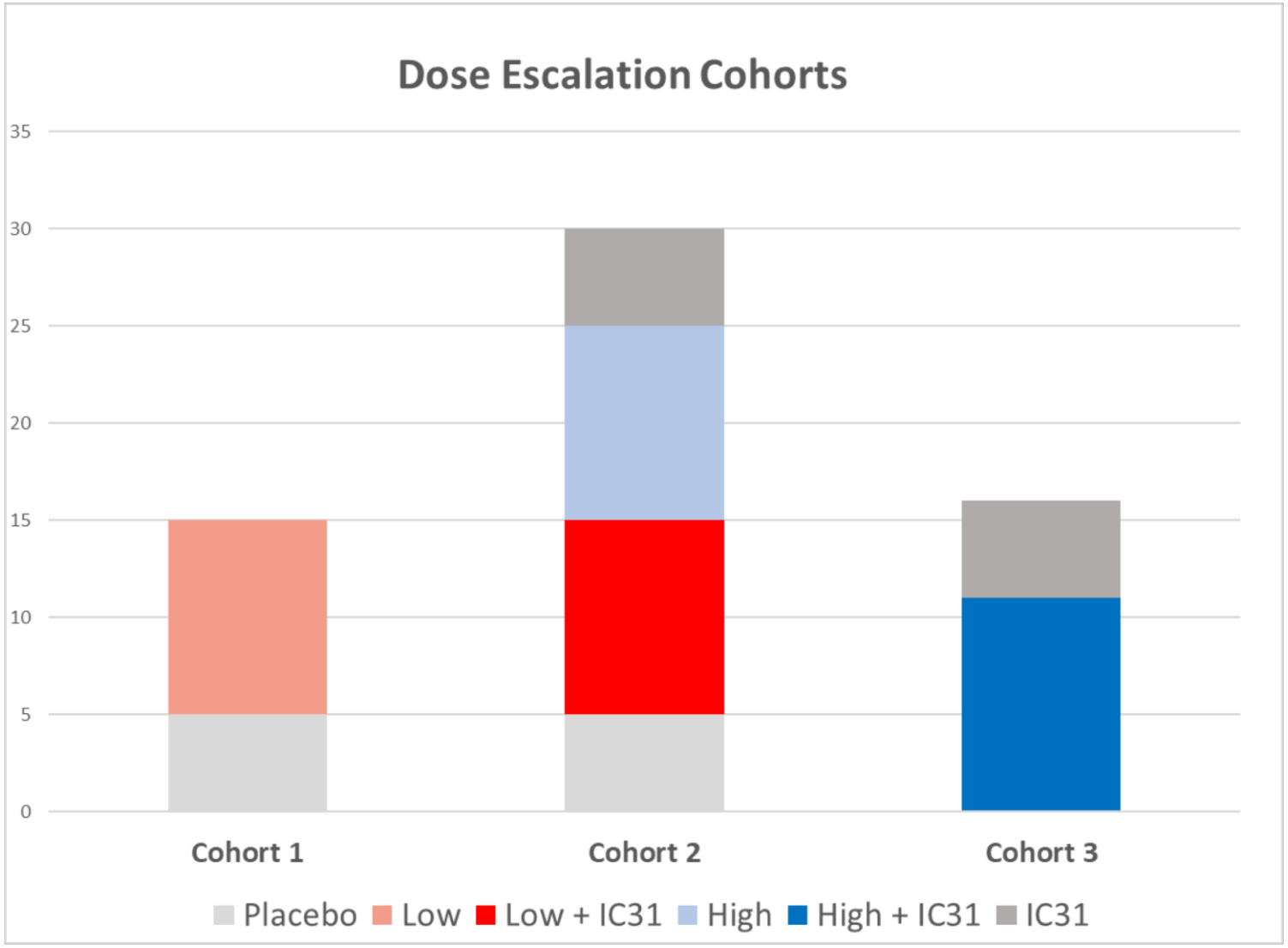
- Safety: Routine labs, AEs, injection site assessment
- Ex-vivo and Cultured ɣ-IFN Elispot
- qHBsAg

Treatment

- 3 double blind dose escalating cohorts enrolled from sites in UK and Korea
- Low or high dose peptides, with or without IC31, IC31 alone and vaccine diluent as placebo
- 3 im injections 28 days apart, followed by 6 month observation



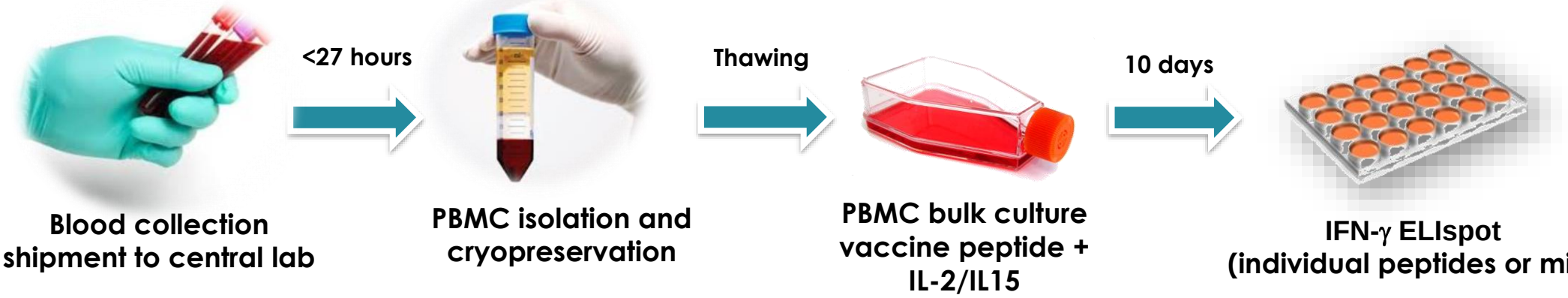
HepTcell Phase 1: Dose Escalation



- Subjects randomized within each cohort as shown
- Sentinel group followed through day 8 before rest of cohort randomized
- Each cohort followed through day 36 (1 week after 2nd dose) before next sentinel group dosed
- Blinded safety review by investigators and medical monitor before next group randomized

Laboratory Methods

IFN-γ ELISpot GCLP assays[1] performed at Altimmune UK



- Samples were analyzed in triplicate with positive and negative controls. Samples that did not meet pre-specified positive control criteria were excluded from the analysis. Resulting spot-forming cell/well were averaged and background counts subtracted to obtain final results in spot-forming cells/10^6 PBMCs.

Viral Assays performed by King's Liver Labs, London UK

- Quantitative HBsAg was measured from serum stored at ≤ -20°C by automated chemiluminescent micropartical immunoassay (Abbott ARCHITECT).

[1]Method by Todryk et al 2009, use in chronic HBV described in Rivino et al J Clin Invest 2018

Baseline Characteristics

	Low (N=10)	Low+IC31 (N=10)	High (N=10)	High+IC31 (N=11)	IC31 (N=10)	Placebo (N =10)
Sex: % Male	90	100	70	73	50	90
Race: % White	10	10	0	0	0	10
% Black	30	10	10	0	0	10
% Asian	50	70	70	100	90	30
% Other/Multi	10	10	20	0	10	50
Age: Median (min-max)	39.5 (33-53)	50 (40-63)	45.5 (41-65)	47 (34-64)	49.5 (40-65)	47.5 (38-57)
Fibroscan: Median (min-max)	4.80 (3.3-6.9)	5.15 (3.5-7.3)	6.10 (3.3-10.0)	4.80 (3.0-6.3)	3.90 (2.6-7.2)	5.80 (3.8-8.2)
Log_{10} HBsAg IU/ml Median (min-max)	2.88 (1.16-3.53)	2.99 (1.56-3.98)	2.80 (-0.49-4.14)	3.02 (2.32-3.75)	3.22 (-1.52 -3.51)	3.77 (1.51-4.24)
ALT U/L: Median (min-max)	22 (12-33)	30 (14-46)	23 (15-55)	17 (10-31)	15 (11-39)	26 (17-37)

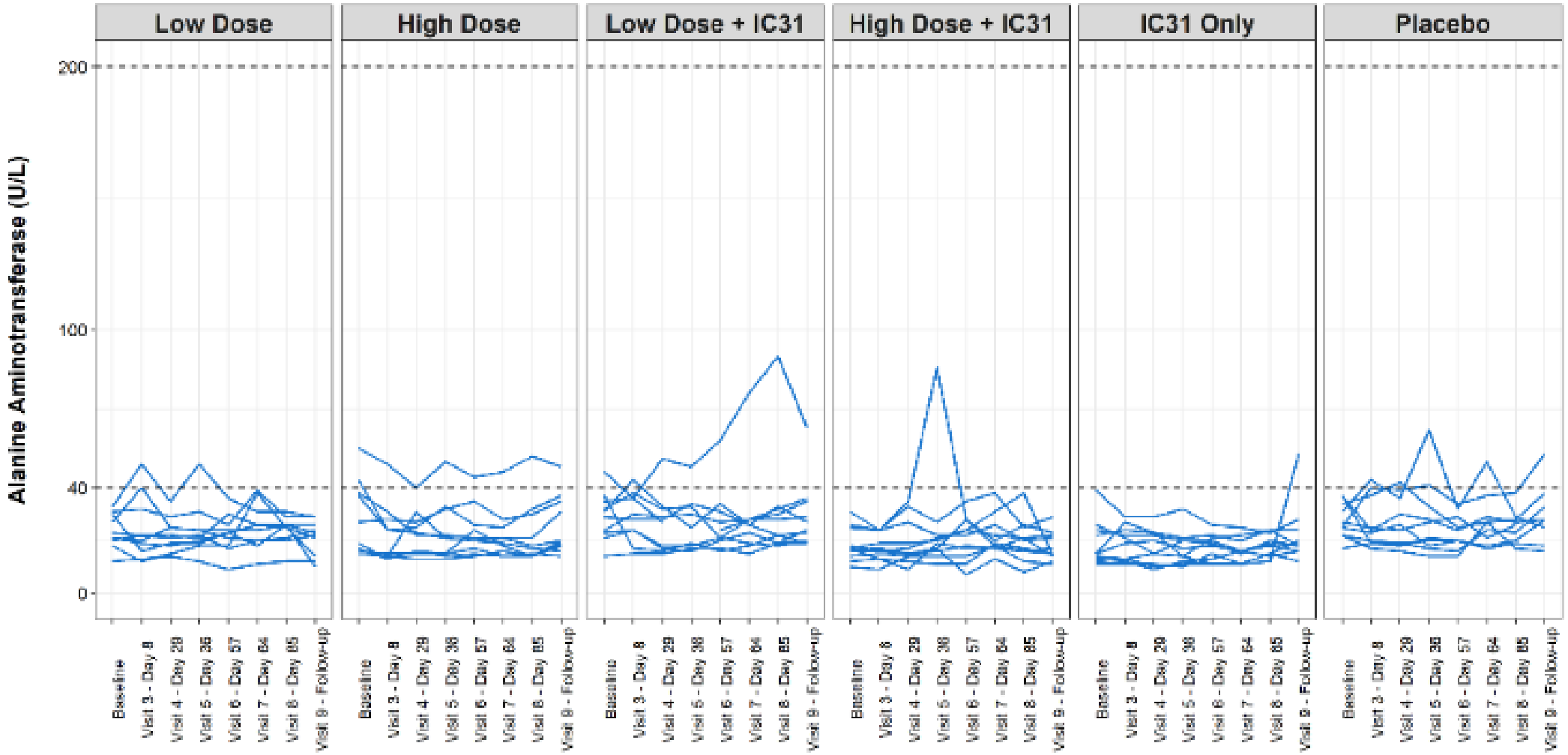
Safety

Investigator Assessed Injection Site Reactions

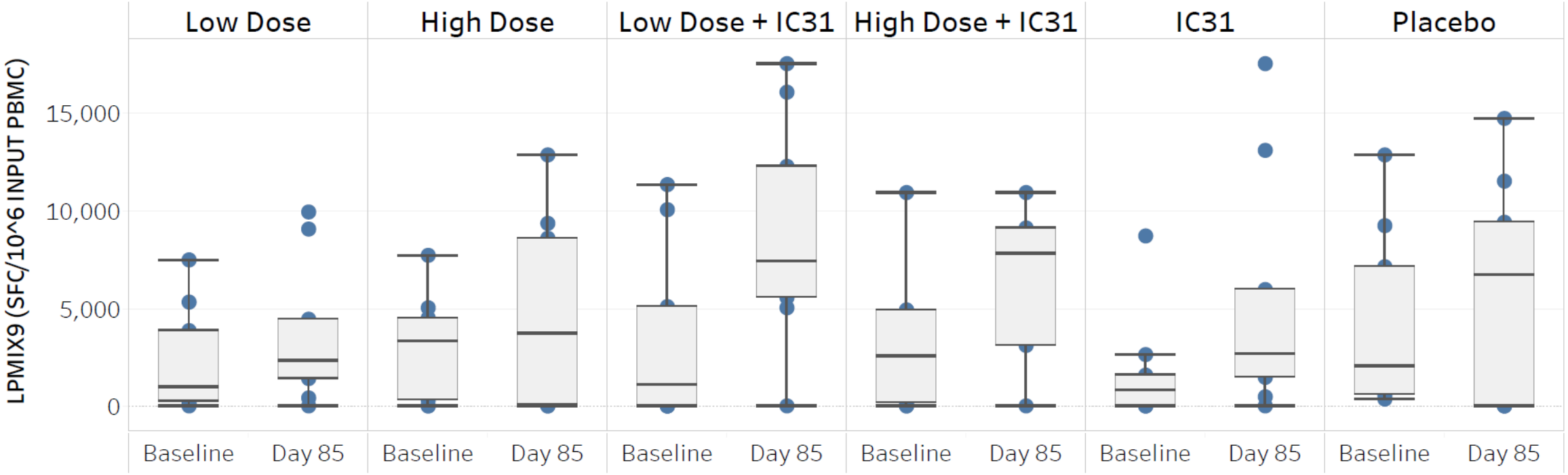
	Low (N=10)	Low+IC31 (N=10)	High (N=10)	High+IC31 (N=11)	IC31 (N=10)	Placebo (N =10)
Any Reaction (%)	60	60	50	46	10	20
Burning (%)	0	30	20	0	0	10
Erythema (%)	0	10	0	9	0	20
Induration (%)	10	0	10	0	10	20
Swelling (%)	20	0	0	0	0	20
Pain (%)	60	30	30	36	0	10
Tenderness (%)	50	40	50	9	0	20

- 1 SAE (infectious colitis between dose 2 and 3) in High+IC31 subject
- No autoimmune events
- No hepatitis flares
- No trends in other AEs
- Injection site reactions were self-limited and mild-moderate except for one patient with severe tenderness in the low+IC31 group

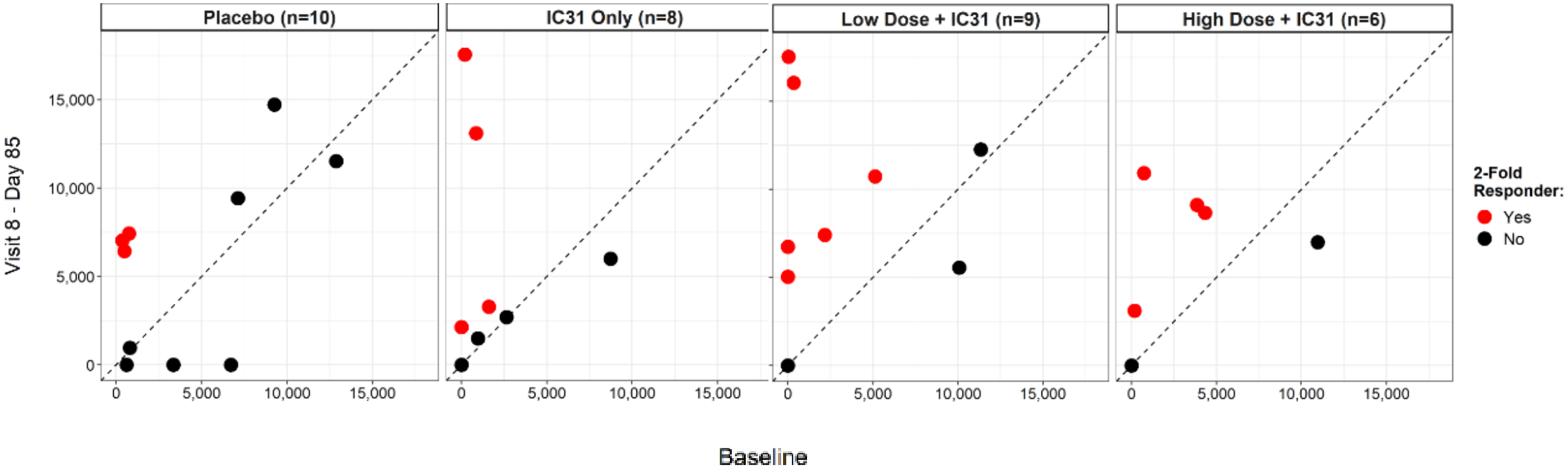
Safety – ALT over time by treatment group



IFN-ɣ ELISPOT: Baseline and Day 85

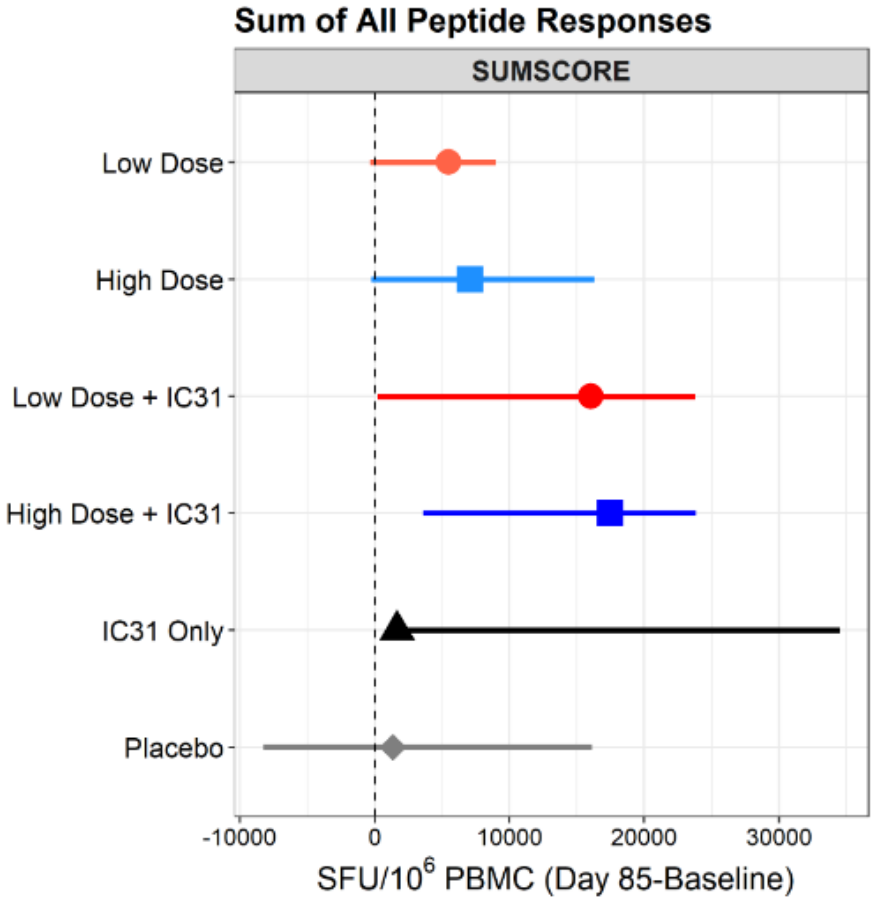


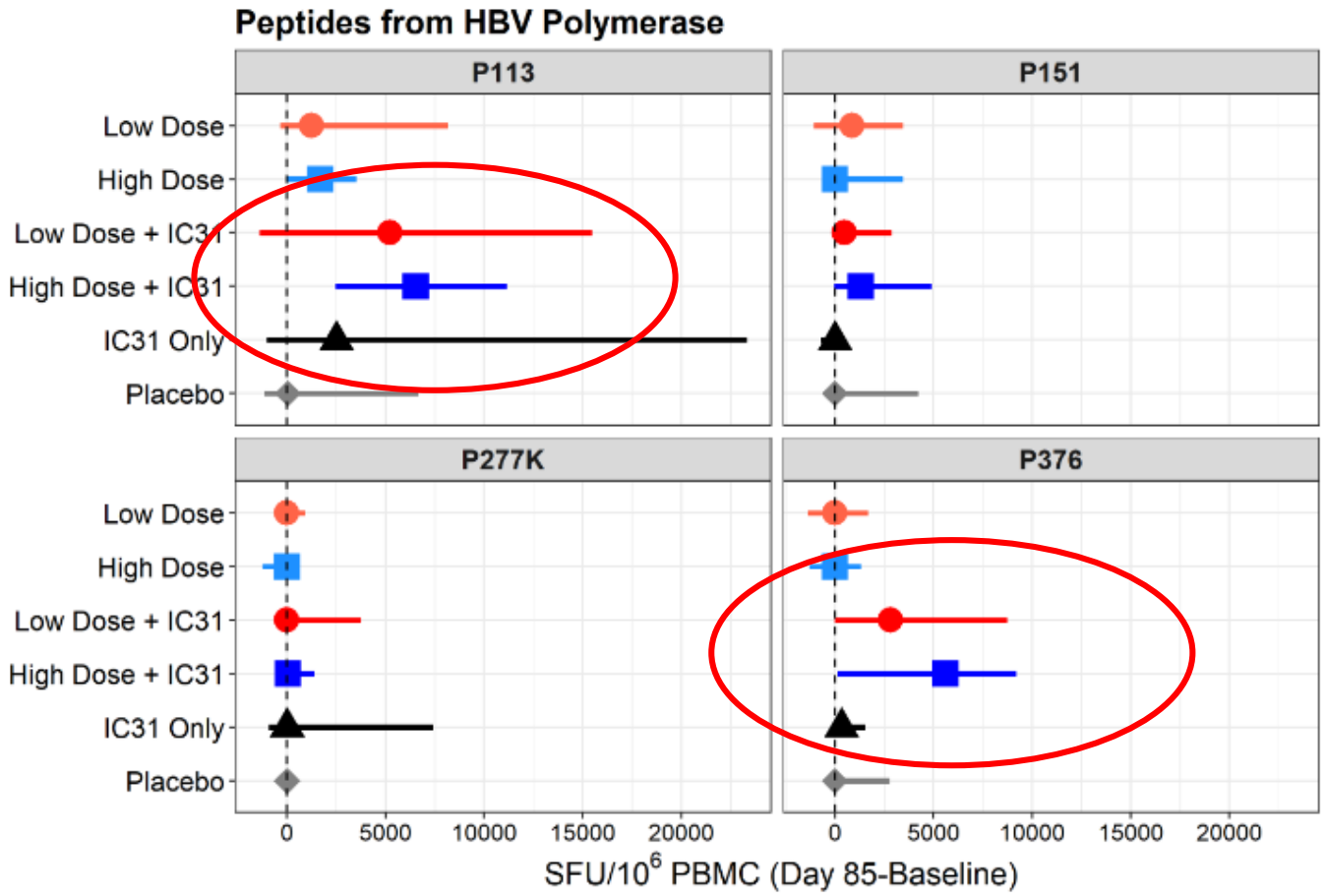
IFN-ɣ ELISPOT: Baseline and Day 85 (peptide mix)



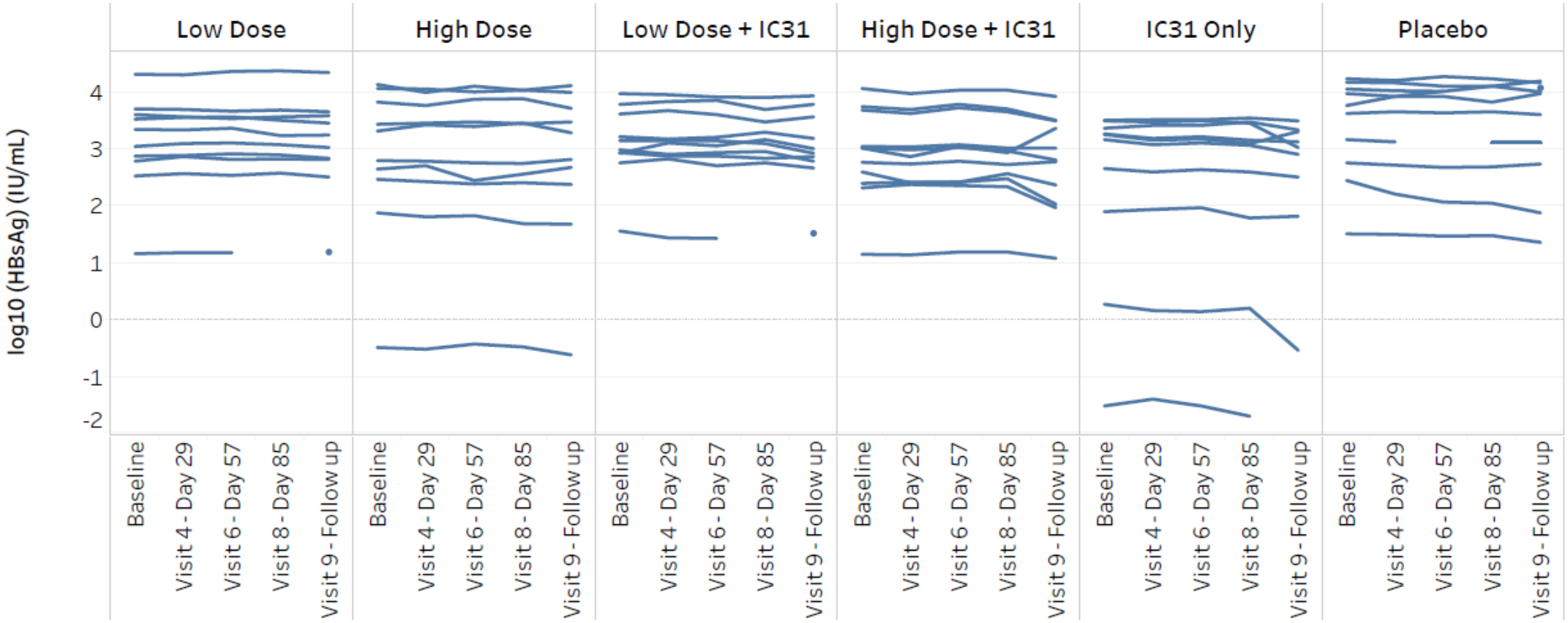
Median Change in IFN-ɣ ELISpot (Immunogenicity Set)

Strongest response from Pol related peptides





Quantitative HBsAg over time by treatment group



HepTcell Phase 1 Clinical Data Summary

- All doses well tolerated and no flares in this well-controlled eAg- population
- Peptides + IC31 resulted in increased HBV specific cellular immune responses
  - Among adjuvanted dose groups, higher dose did not appear to increase the response, consistent with other T-cell vaccines[1,2]
  - Responses predominantly to peptides derived from pol, which may predict successful treatment discontinuation[3]
  - Some response to adjuvant only which has been described previously[4]—may be due to improved immune responses against HBV antigens in circulation
- No change noted in antiviral markers above placebo

[1]Bernstein et al. J Infect Dis 2017

[2]Rhodes et al. Vaccine 2016

[3]Rivino et al. J Clin Invest 2018

[4]Xu et al. J Hepatol 2013

HepTcell Phase 1 Conclusion and Phase 2 Plans

Safety and immunogenicity support continued evaluation

- Broader HBV patient populations including eAg+ and chronic carriers
- Longer dosing periods
- In combination with novel directly acting antivirals

Acknowledgements

Investigators and their patients

United Kingdom

- Mark Thursz, Imperial College Healthcare NHS Trust
- Kosh Agarwal, Kings College Hospital NHS Trust
- Daniel Forton, St. Georges Hospital
- Patrick Kennedy, Royal London Hospital
- William Rosenberg, Royal Free London NHS Trust
- Stephen Ryder, Nottingham University Hospital NHS Trust
- David Mutimer, University Hospitals Birmingham NHS Trust
- Sulleman Moreea, Bradford Teaching Hospitals NHS Trust
- Andrew Ustianowski, The Pennine Acute Hospitals, NHS Trust
- Peter Collins, University Hospitals Bristol NHS Trust

South Korea

- Young-Suk Lim, Asan Medical Center
- Seung Woon Paik, Samsung Medical Center
- Yoon Jun Kim, Seoul National University Hospital
- Jong Eun Yeon, Korea University Guro Hospital
- Mong Cho, Pusan National University Yangsan Hospital
- Jeong Heo, Pusan National University Hospital
- Byoung Kuk Jang, Keimyung University Dongsan Medical Center
- Jeong Won Jang, Seoul St. Mary's Hospital, The Catholic University of Korea
- Won Kim, SMG-SNU Boramae Medical Center
- Jun Yong Park, Yonsei University Health System Severance Hospital
- Won Young Tak, Kyungpook National University Hospital

Altimmune Team (Past and Present)