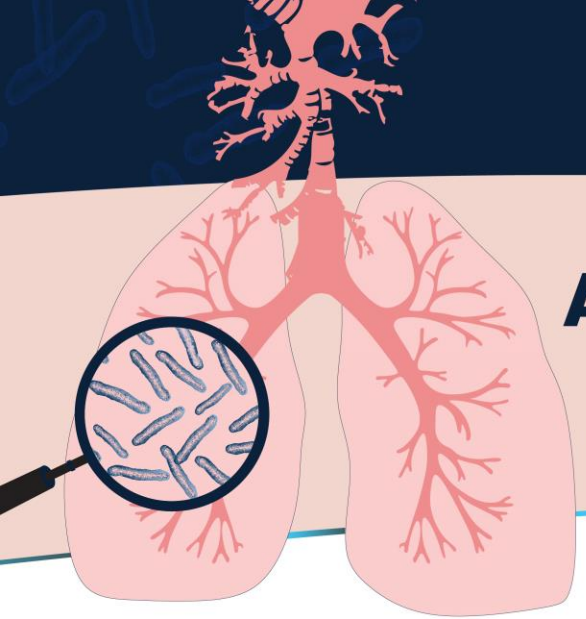


Accelerating progress to end TB

8th SA TB Conference
04 - 07June 2024
Durban ICC

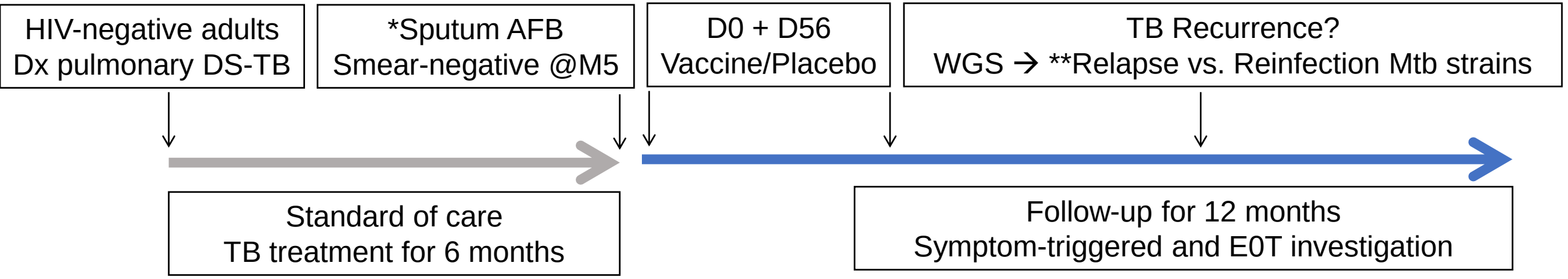
H56:IC31 vaccine immunogenicity & Correlates analysis

05 June 2024

Anele Gela, PhD

South African Tuberculosis Vaccine Initiative, University of Cape Town

Study design:



6 clinical sites in SA and Tanzania

Design Assumptions

Recurrence rate in placebo arm	4% per year
Vaccine Efficacy (POR)	60%
Power	80%
Sample size	450 per arm
Expected primary TB endpoints	23

*Programmatic definition of treatment cure

** Mtb isolates from diagnostic & recurrence sputa differing by ≤5 SNPs were considered relapse

Slide courtesy of Mark Hatherill

Study Endpoints:

Primary efficacy endpoint:

Recurrent TB (due to relapse, reinfection or indeterminate), defined as MGIT culture-confirmed pulmonary TB occurring after D70 (14 days after second vaccination) through 12 months.

Secondary efficacy endpoints

Recurrent TB due to:

- **Relapse of the original Mtb strain**, differing by ≤5 SNPs from diagnostic isolate
- **Reinfection with a different Mtb strain,** differing by >5 SNPs from diagnostic isolate

Secondary safety endpoints: Solicited injection site adverse events, systemic adverse events, serious adverse events (SAE) and adverse events of special interest (AESI)

Secondary immunogenicity endpoints: Antigen-specific, cell-mediated immune responses and humoral anti-H56 IgG responses

POR TB Consortium

Immunogenicity

Primary objective:

- CD4 T-cells expressing any combination of IL-2, IFN-γ, TNF, and/or IL-17 (i.e. the total cytokine response) at Day 0 and Day 70 in each study arm.
- CD4 T-cells co-expressing IL-2 and TNF
- CD4 T-cells co-expressing IL-2, IFN-γ, and TNF
- CD8 T-cells expressing any combination of IL-2, IFN-γ, TNF, and/or IL-17 (i.e. the total cytokine response) at Day 0 and Day 70 in each study arm

H56:IC31

Placebo

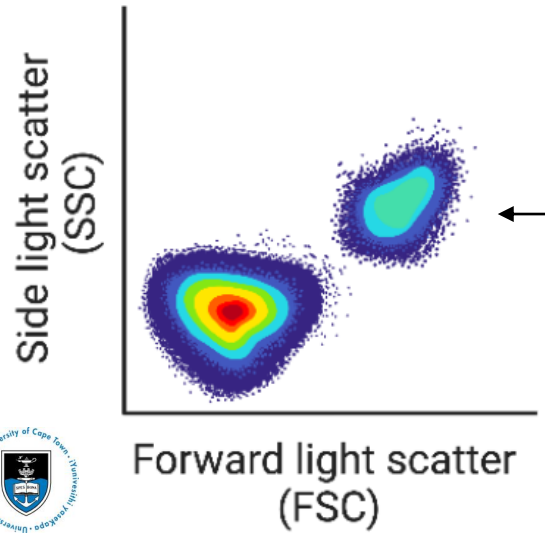
Stimulate with H56 antigens for 7 hours
37°C, 5% CO_2

↓

Add BFA
Stimulate for 5 hours
37°C, 5% CO_2

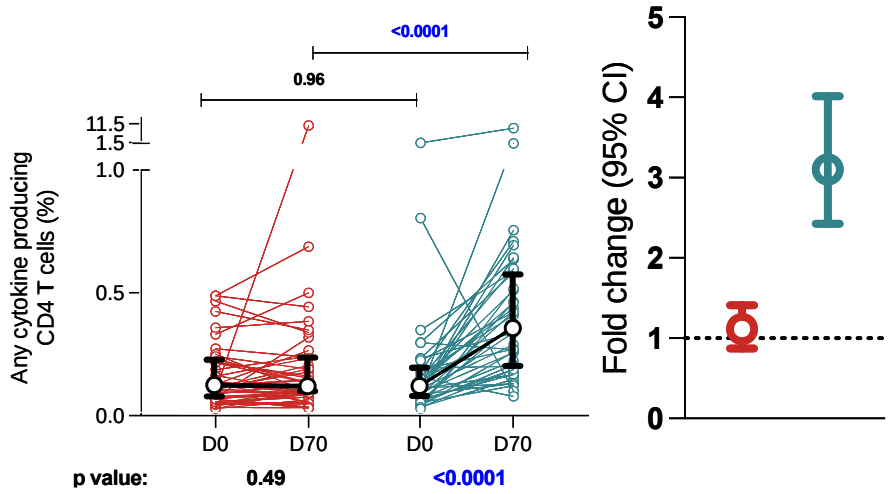
↓

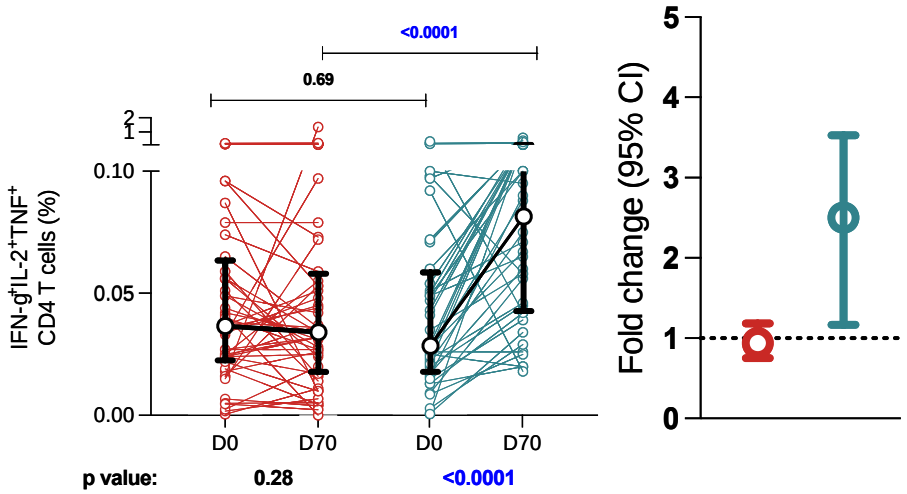
Harvest
Red cell lysis
Cryopreserve



	Marker	Function
Primary	**CD3**	Lineage
	CD4	Lineage
	CD8	Lineage
	IFN-γ	Th1 cytokine
	TNF	Th1 cytokine
	IL-2	Th1 cytokine
	IL-17	Th17 cytokine
	CCR7	Memory
Exploratory	**CD45RA**	Memory
	CD153	Activation marker
	HLA-DR	Activation marker
	Ki67	Proliferation
	PD1	T cell differentiation
	CD103	Mucosal tissue retention

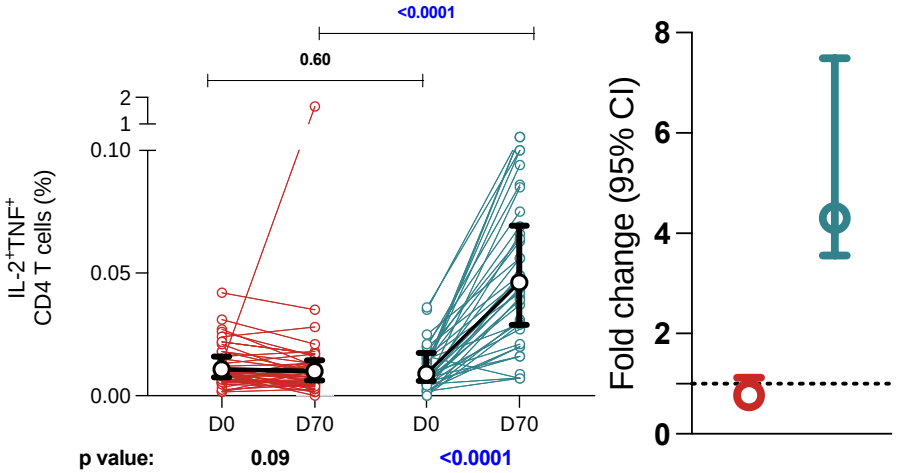
Primary outcomes:

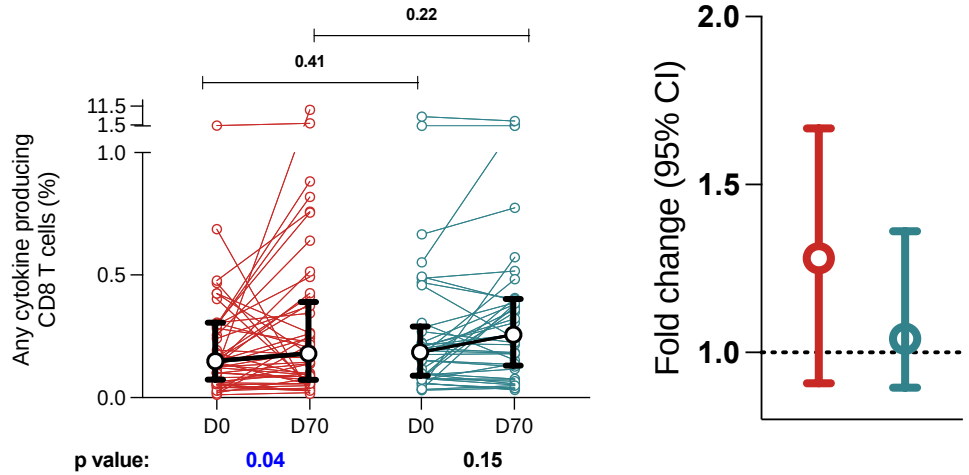




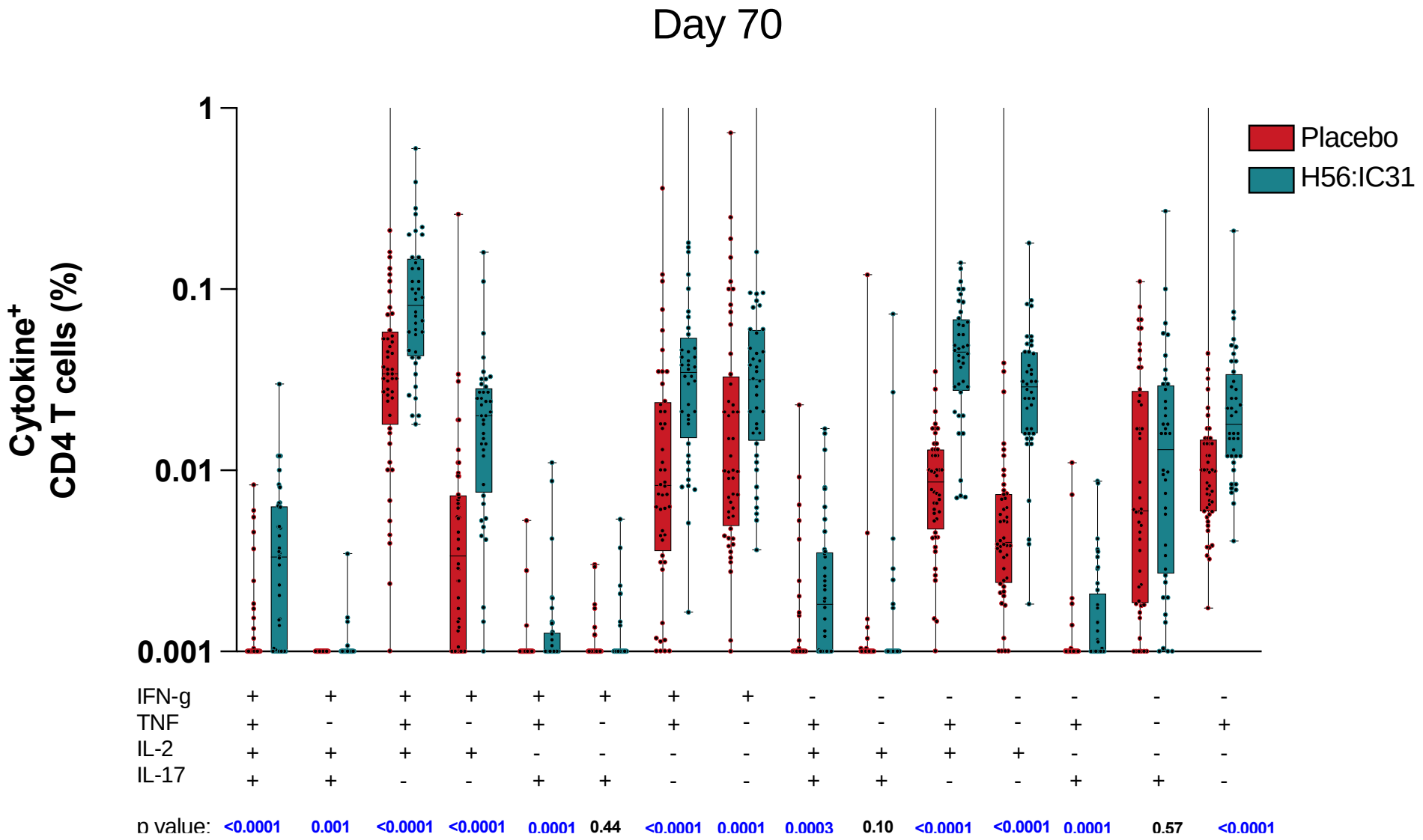
Placebo

H56:IC31

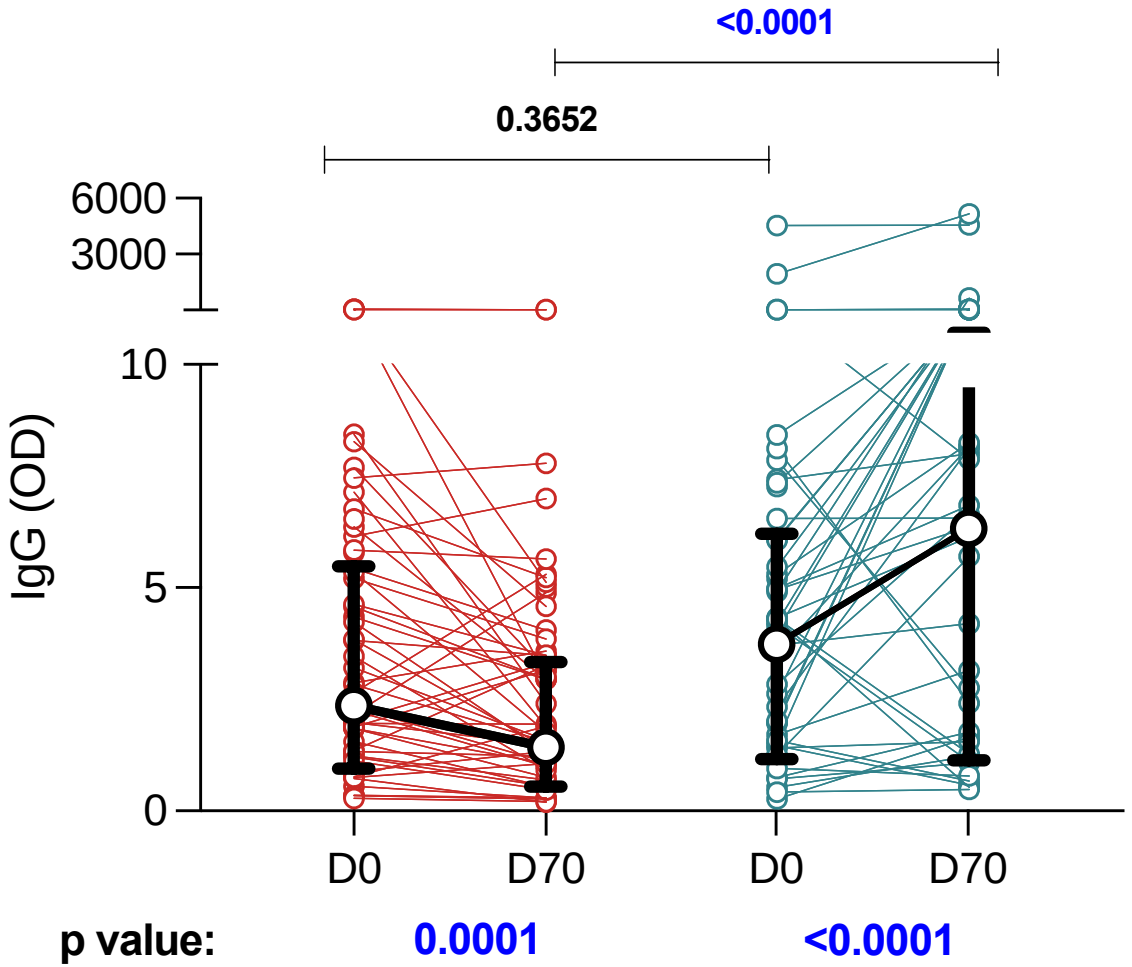


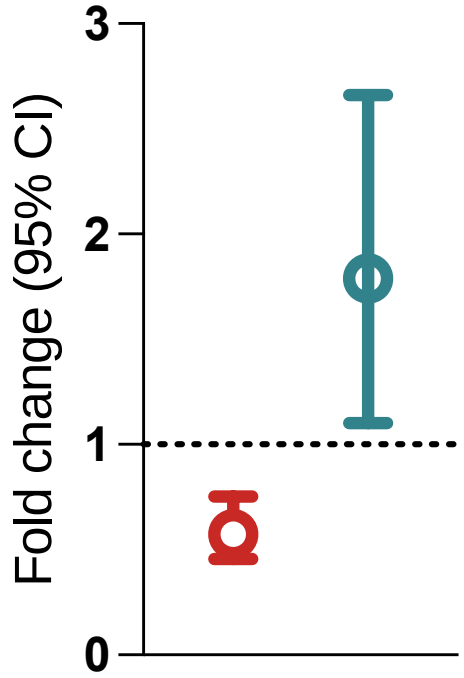


Exploratory outcomes: CD4 T cell subsets

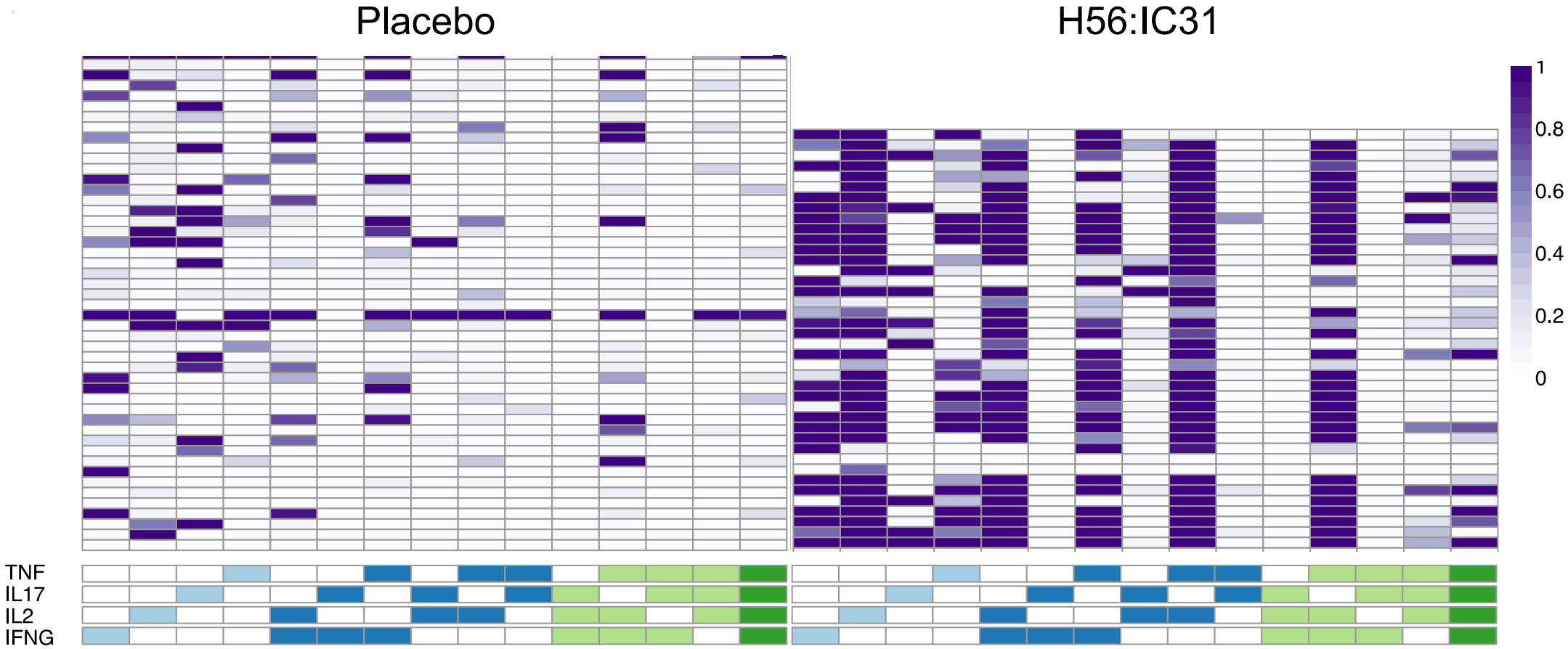


Exploratory outcomes: antibody responses

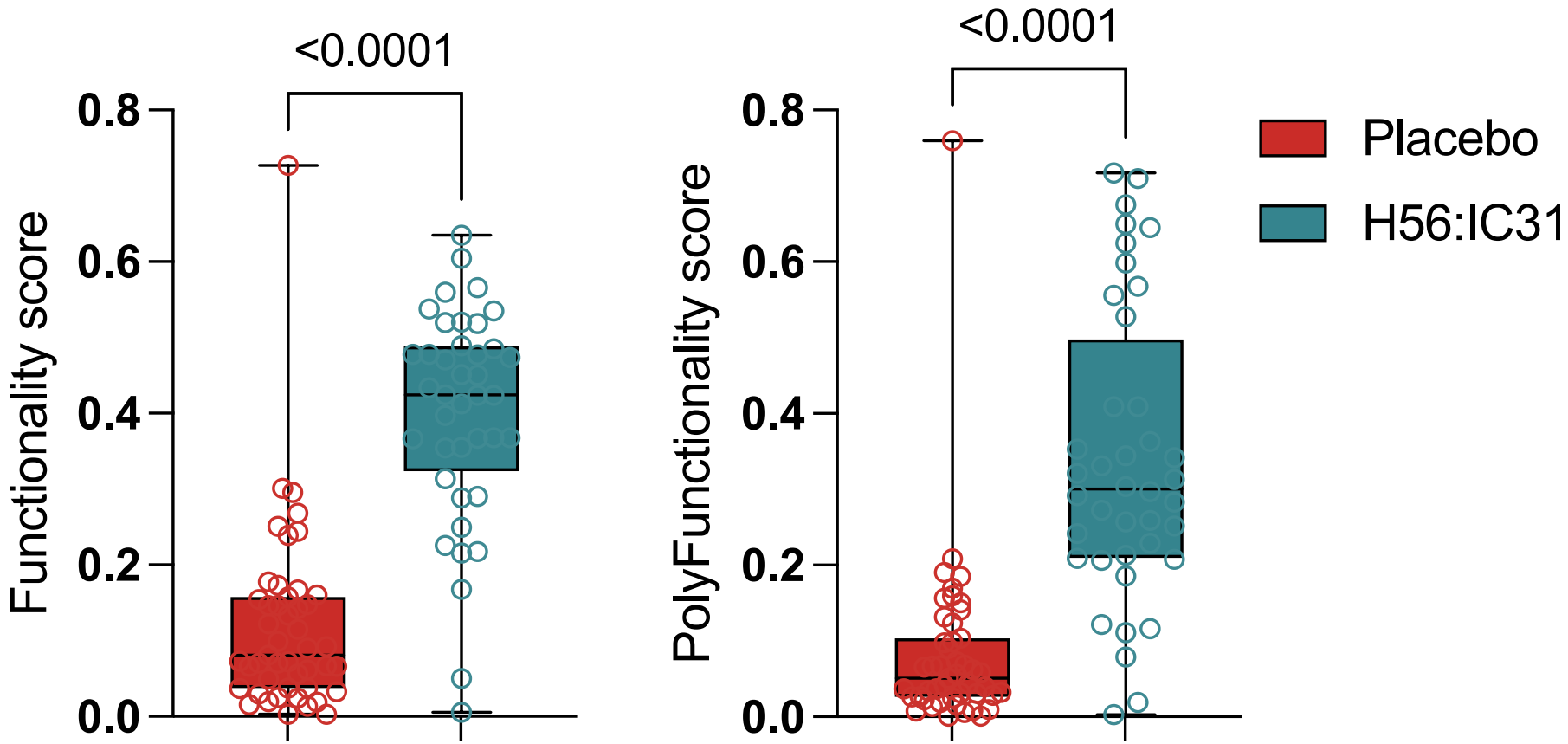




Exploratory outcomes: COMPASS



Exploratory outcomes: COMPASS



Interpretation:

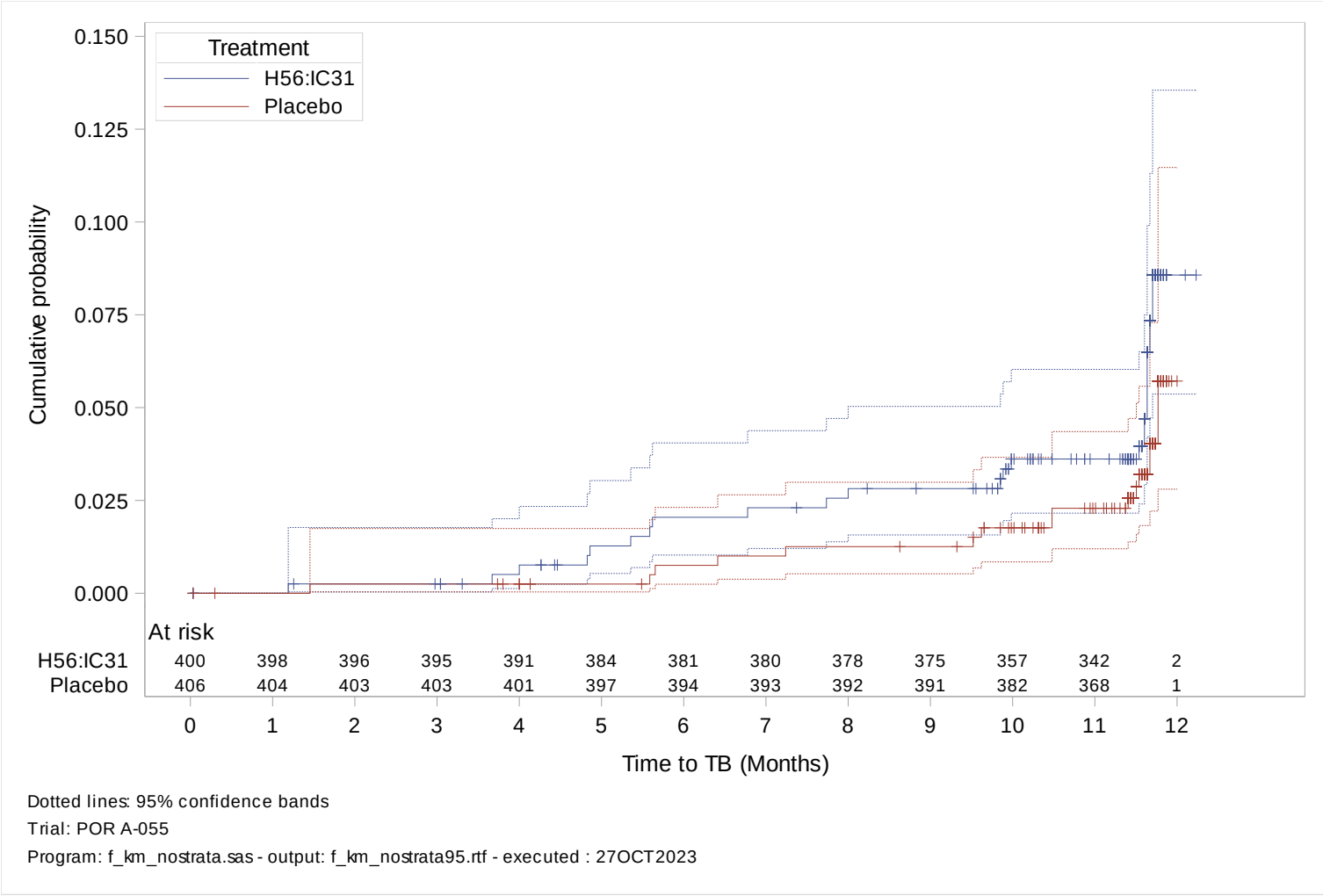
- We found that H56:IC31 was immunogenic in patients who were successfully treated for drug-susceptible TB.

- H56-induced responses were predominantly comprised of Th1-cytokine-expressing CD4 T cells that mostly co-expressed IFN-γ, TNF and IL-2.

- H56-specific CD8 T cells were not modulated by vaccination

H56:IC31 vaccination did not protect against TB recurrence in the A-055 POR trial

TB recurrence		
H56:IC31 (n = 400)	23	VE = -73.8% (95%CI: -246.9 to 9.8) p-value = 0.10
Placebo (n = 406)	14	



Dotted lines: 95% confidence bands
Trial: POR A-055
Program: f_km_nostrata.sas - output: f_km_nostrata95.rtf - executed : 27OCT2023

Questions and hypotheses:

	Recurrence	Relapse	Reinfection
H56:IC31	23	12	8
Placebo	14	6	7

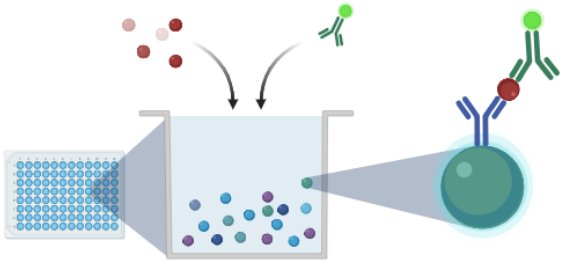
Is it possible that H56:IC31 vaccination increased the risk of TB recurrence, and in particular TB relapse, in the A-055 trial?

We propose that subset of participants are at high risk of TB relapse after TB treatment completion, irrespective of H56:IC31 vaccination

Hypothesis:

- *Recurrent TB cases will have significantly higher transcriptomic signature scores than controls, indicating that before vaccination they were already at risk of relapse.*
- *Epigenetic modifications following successful TB treatment are associated with increased risk of recurrent TB disease*
- *DNA hypermethylation is negatively associated with the magnitude of mycobacteria-specific T cell responses before and after H56:IC31 vaccination.*

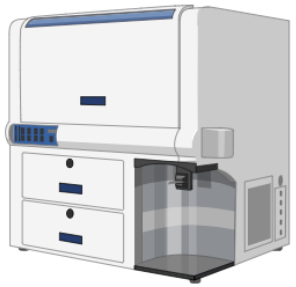
Experimental workflow:



Multiplex protein Detection assay

Stimulated PBMC

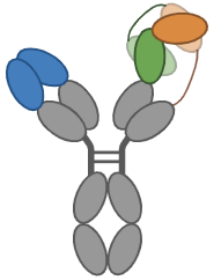
Ex vivo plasma



PBMCs

D0
D70
STB

Plasma



Serology

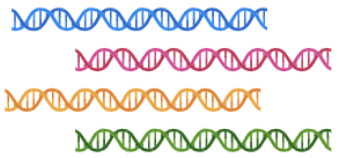
Flow cytometry

Ex vivo immunophenotyping

Whole blood fixed cells

D0
STB

Whole blood RNA



Microfluidic qPCR
Bulk RNAseq

Acknowledgements

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