CLINICAL DEVELOPMENT OF TUBERCULOSIS SUBUNIT VACCINE H1IC

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Seventh EDCTP Forum
Berlin July 1 2014

DISCOVERY OF ANTIGENS

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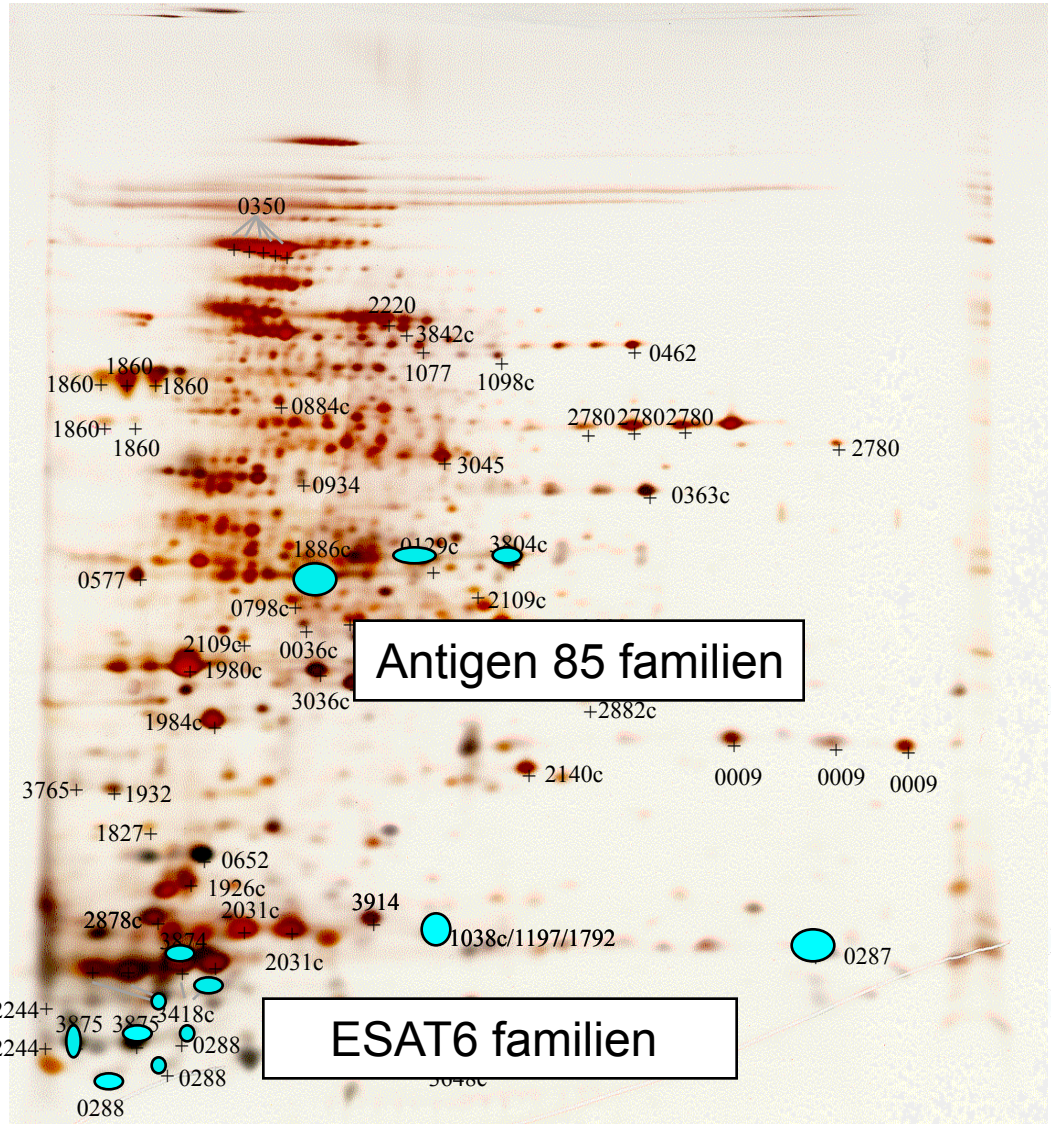
>300 dif. proteins



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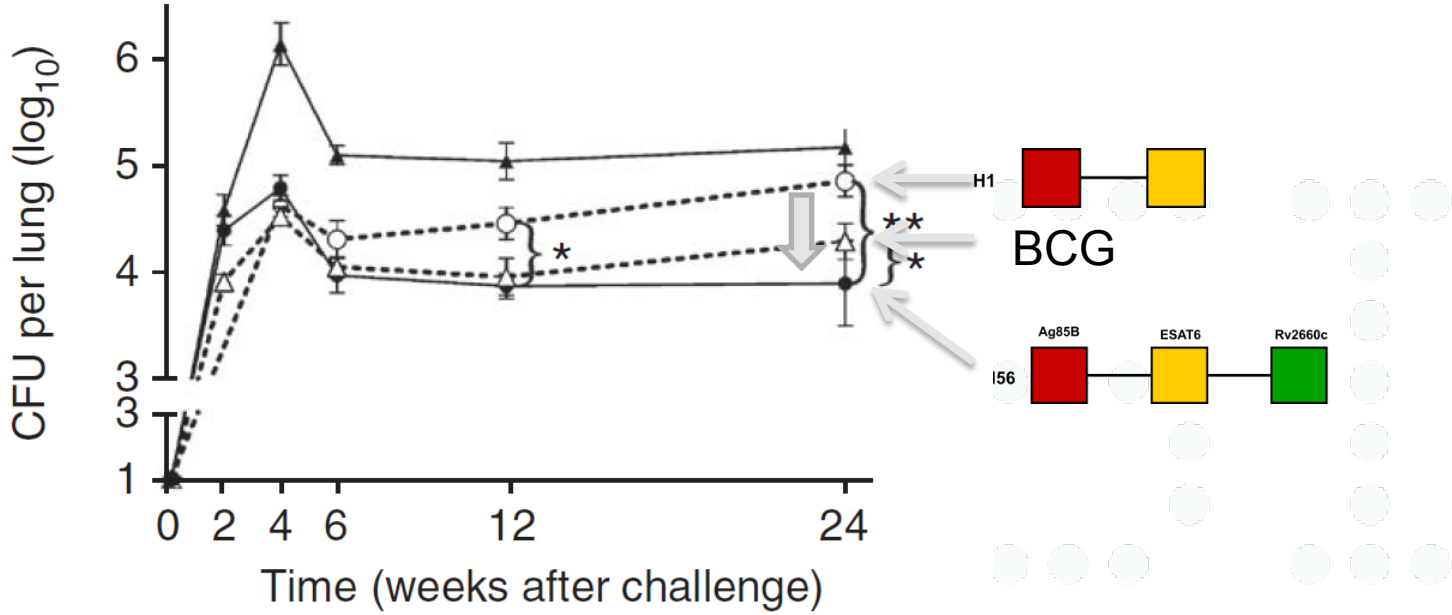
H1 – H56

Substantial pre-clinical data demonstrated H56 superiority
>> decision to take H56 into clinic



Aagaard et al, Nature Medicine 2011

H1:IC

Ag85B ESAT-6

H56:IC

Ag85B ESAT-6 Rv2660

Prevent acute TB disease as well as re-activation of existing latent infection

- Adolescents and young adults in a largely BCG vaccinated population
- With and without latent infection
- Safe in HIV+ and TB patients

AERAS GLOBAL TB VACCINE FOUNDATION

EDCTP

TBVI Tuberculosis Vaccine Initiative

BILL & MELINDA GATES foundation

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H1/H56IC IN CLINICAL TRIALS

H1IC	H56IC
THYB-01 *Phase Ia N=36*	
THYB-02 *Phase Ib N=20*	
THYB-03 *Phase Ic N= 39*	C-032 *Phase Ia N=25*
THYB-04 *Phase IIa N=240*	C-035 *Phase I/II N= 98*
THYB-05 *Phase IIa N=48*	C-037 *Phase IIa N= 72*

IC= IC31®

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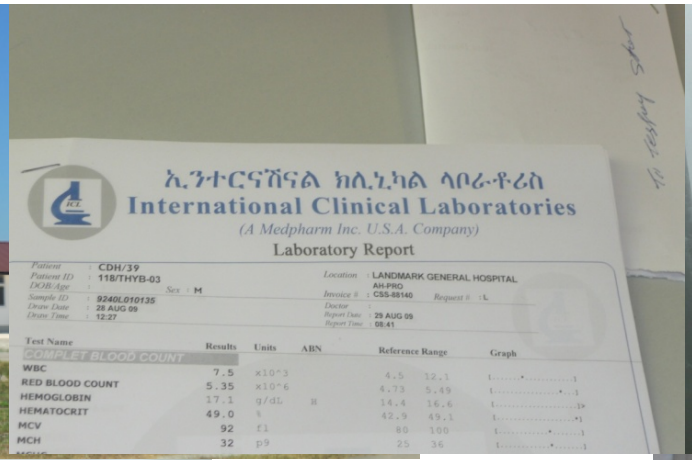
PREPARING CLINICAL SITES



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THYB-03, PHASE I CLINICAL TRIAL

- AHRI Ethiopia
- QF- and QF+ Adults
- 39 out of 48 included in study
- FVFV December 2008
- LVLV April 2010

Study Group	Dose (H1 mcg/IC31 nmol)	population	N	N included in study
1	50/0	naive	12	12
2	50/500	naive	12	12
3	50/500	BCG vaccinated	12	3
4	50/500	QF+	12	12
Total			48	39

2 possible releated SAE

THYB-04, PHASE II CLINICAL TRIAL

- SATVI South Africa
- QF- and QF+ Adolescents 12-18 years
- First vaccination August 2012
- Last vaccination July 2013

Study Group	Dose 1 (H1 mcg/IC31 nmol)	Dose 2 (H1 mcg/IC31 nmol)	Treatment Assignment	
1 -LTBI	15/500	15/500	30	120 QF-
2 -LTBI	50/500	50/500	30	
3 -LTBI	15/500	Placebo	30	
4 -LTBI	50/500	Placebo	30	
5 +LTBI	15/500	15/500	30	120 QF+
6 +LTBI	50/500	50/500	30	
7 +LTBI	15/500	Placebo	30	
8 +LTBI	50/500	Placebo	30	
Total			240	

No releated SAE

THYB-05, PHASE II CLINICAL TRIAL

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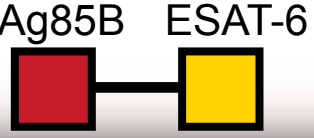
- Johannesburg SA and Bagamoyo TZ
- HIV+ Adults with CD4+ T cells >350 cells/mio
- 20/48 QF+ at inclusion
- Data locked Q2 2013

Study Group	Dose (H1 mcg/IC31 nmol)	Number of Doses	Treatment Assignment		
			H1:IC31	Placebo	Total
1	50/500	2	20	4	**24**
2	50/500	2	20	4	**24**
Total			**40**	**8**	**48**

No releated SAE

BRIEF SAFETY SUMMERY H1IC



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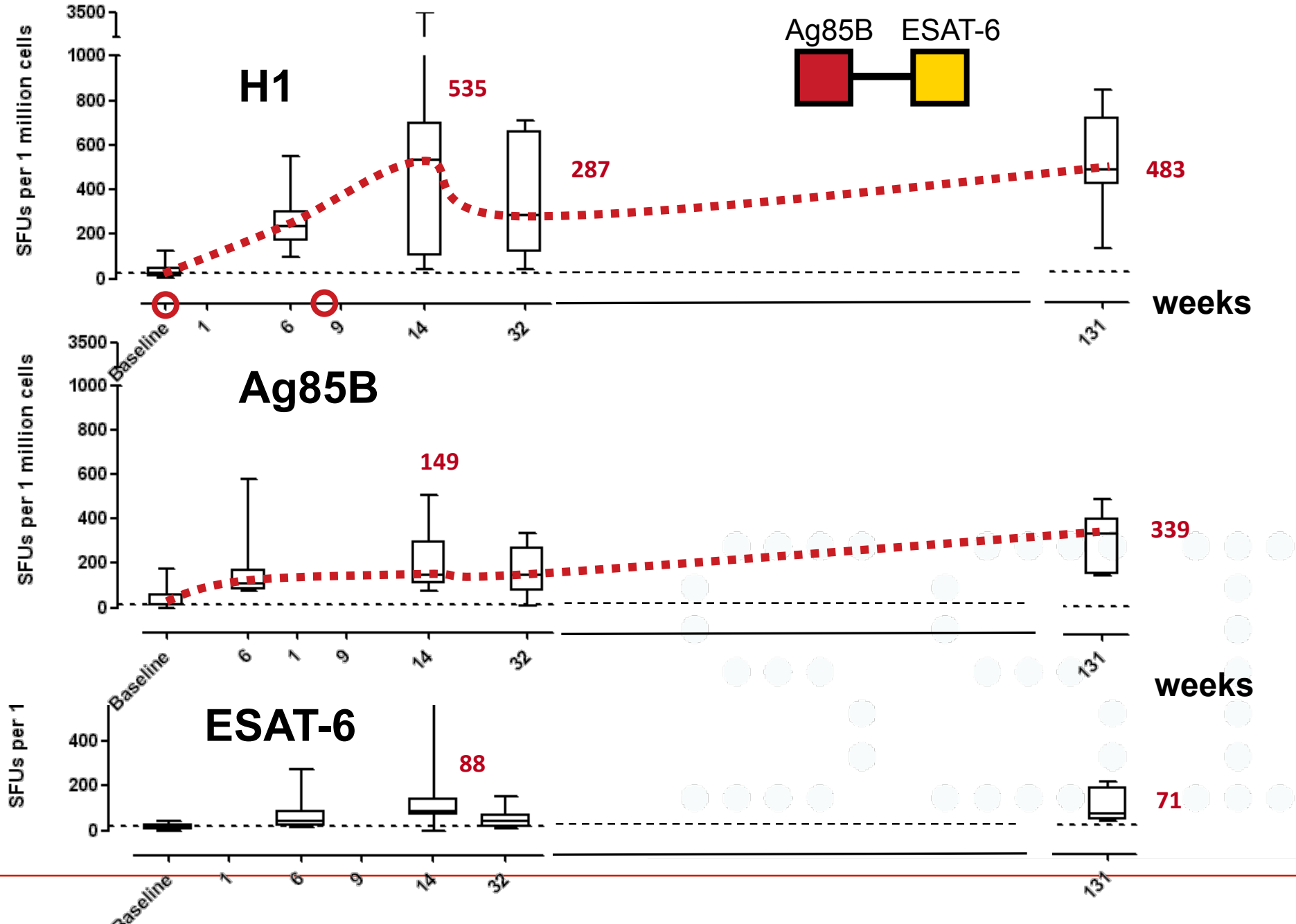
The vaccine has been tested in 375 volunteers

Main local reactions	Grade	Main Systemic reactions	Grade
Injection site pain	Mild/moderate	Headaches	Mild/moderate
Stiffness	Mild/moderate	Fatique	Mild/moderate
Skin irritations	Mild/moderate	Myalgia	Mild/moderate

Long term memory in BCG naïve… (THYB-01)



THYB04 – PRELIMINARY RESULTS

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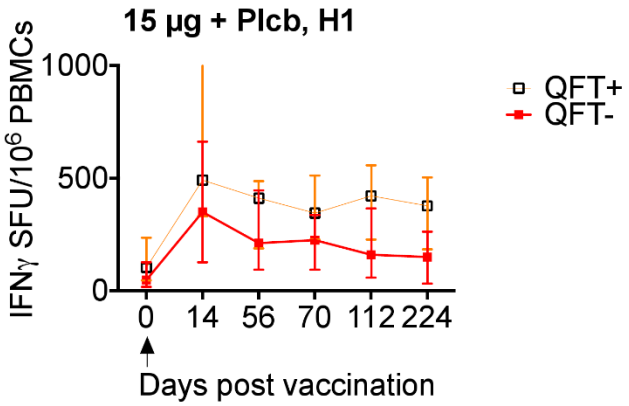
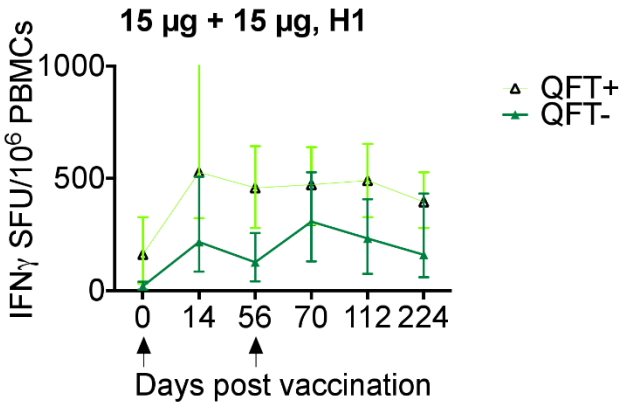
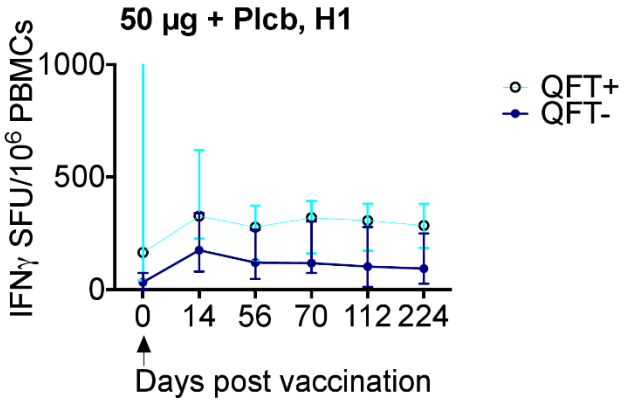
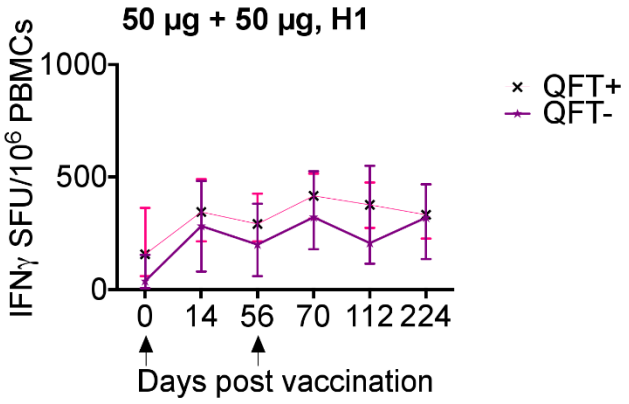
- Immunogenic in all groups against H1, ESAT-6 and Ag85B
- Similar kinetics in all groups
- QFT+ve higher magnitude at all timepoints
- Responses sustained
- ELISPOT data, 50 ug was not superior to 15 ug, dose selection should be based on ICS flow data









THYB05 – IMMUNOGENICITY IN HIV INFECTED

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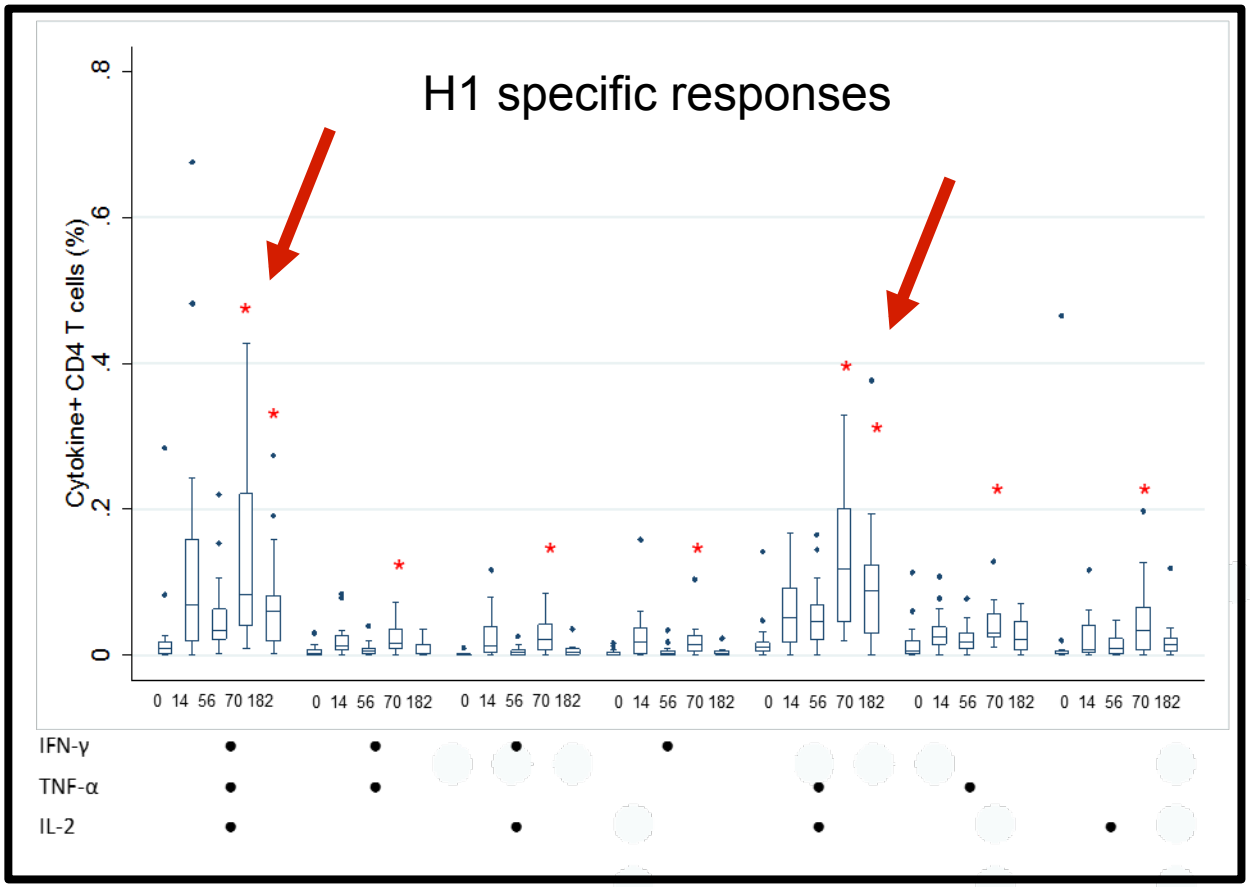
- 48 HIV infected adults, CD4 >350/mm3, 40% QFT+
- Aurum inst, ZA, Bagamoyo TZ Immunogenicity data only from Bagamoyo site (20+4), aquired at SATVI
- Vaccine arm: (n=40)
  50ug H1:IC31; day 0 and 56
- Assays: ICS flow,
  ELISPOT failed QC



- Findings
  - CD4+ cell responses to H1, Ag85B and ESAT-6
  - Dominance of CD4+ IL-2+/TNF-α+ and IFN-γ+/IL-2+/TNF-α+
  - ~~No significant induction of IgG~~

(Reither et al submitted)

2013 - 2020 H1/H56 Trial Schedule

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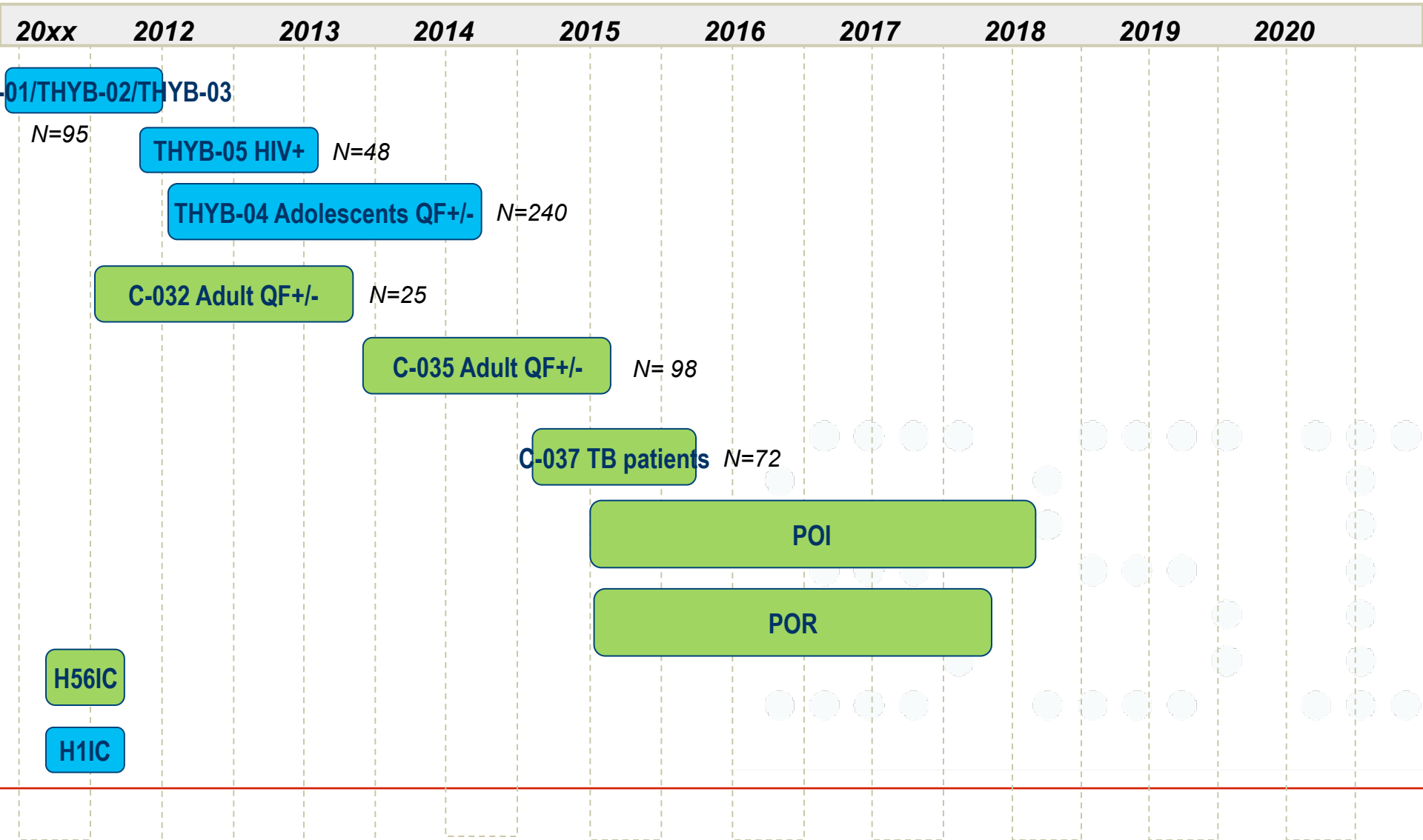

CONCLUSIONS

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- *Safety*

  Most of Adverse events observed in all populations (Adult, adolescents, naïve, BCG vaccinated, HIV+, QF+) are mild and a few moderate. In general the Adverse Events were short lasting.

- *Immunogenicity*

  The vaccine is clearly immunogenic – also in HIV+.
  15 µg antigen seems to be superior compared to 50 µg
  H1IC has shown to induce a long-term (2.5 years) memory response to the vaccine

- *Future Clinical development*

  H56IC will continue in clinical development. H1IC data has been and will be used as supportive data.

LESSONS LEARNED DURING EDCTP GRANT PERIOD

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- **Continued** support for already build capacity is important
- Include funds for support personal such as logistics manager or financial manager into grant application
- Training of staff is important
- **Datamanegement and statistics** should be a focus area
- Data analysis and subsequent reporting is time consuming and may be underestimated
- SAP is a important document
- Include access to a statistician (GCP demand)
- **Language** barrieres
- Pair an experienced trial site with a less experienced site (**mentor**)
- **Cultural** understanding between countries

ACKNOWLEDGEMENTS

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SATVI

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