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Prevention of infection with *Mycobacterium tuberculosis* by H4:IC31 vaccination or BCG revaccination in healthy adolescents: results of a randomized controlled trial (NCT02075203)

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Background & Rationale

Lack validated preclinical models, immune correlates of vaccine-mediated protection

Prevention of TB disease (POD) efficacy trials large, long and costly

Primary BCG vaccination partial protection (19%) against *M.tb* infection

Roy BMJ 2014

Can (re)vaccination prevent *M.tb* infection in a high transmission setting?

- *M.tb* infection >10-fold frequency TB disease
- Prevention of Infection (POI) trial shorter, smaller, less costly vs POD

Hawn MMBR 2014

Can POI trials be used as a decision-making tool for TB vaccine development?

- candidate vaccine up/down selection
- trigger expansion POD efficacy trials

Ellis Tuberculosis 2015

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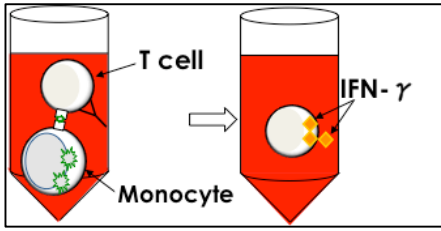
Background & Rationale



Acquisition, persistence and clearance of *M.tb* infection cannot be measured directly

Interferon-gamma release assays (IGRA) = indirect measure of immune sensitization to *M.tb*
IGRA more specific than TST *Pai Clin Microbiol Rev 2014*

IGRA conversion negative → positive ≈ increased risk TB disease
Andrews AJRCCM 2015

Human, animal studies TST reversion positive → negative ≈ decreased risk of TB disease
Hawn MMBR 2014
Dharmadhikari Tuberculosis 2011

Clinical significance of IGRA reversion unclear *Andrews AJRCCM 2012*

Sustained IGRA conversion more likely associated with sustained *M.tb* infection, increased risk TB disease, than transient IGRA conversion with reversion

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Background & Rationale

Aimed to evaluate safety, immunogenicity, and prevention of initial and sustained QuantiFERON-TB Gold In-tube (QFT) conversion by H4:IC31® or BCG revaccination in healthy South African adolescents in a high TB transmission setting

Demonstration of efficacy

→ seek immune correlates of protection against *M.tb* infection

→ utility of POI design for up/down selection of TB vaccine candidates

→ impetus for larger trials to test POD vaccine efficacy in *M.tb*-uninfected populations

Proviso:

2 previous large randomized trials: no overall benefit of BCG revaccination for POD

Did not screen *M.tb* infection status or measure acquisition

33% efficacy in subset of Brazilian children 7-11 years

Rodrigues Lancet 2005
Barreto Vaccine 2011
Karonga PTG Lancet 1996

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Trial Design

Randomized, placebo-controlled, partially-blinded

990 healthy, HIV-uninfected, QFT-negative, adolescents (12-17 years)
BCG vaccinated in infancy
Excluded: Previous TB disease, household TB contact
2 sites (SATVI, Worcester; Desmond Tutu HIV Centre, Cape Town)

3 arms, randomized 1:1:1

Double-blind intramuscular injection (D0 and D56)
Saline placebo
OR
H4:IC31® (15µg H4:500nmol IC31®)
OR
Open-label intradermal injection (D0)
BCG Vaccine (Statens Serum Institut) (2-8 x 10^5 CFU)

H4 (Sanofi Pasteur) subunit vaccine (mycobacterial antigens Ag85B, TB10.4)
IC31® adjuvant (Valneva)
H4:IC31® protection in pre-clinical models, safe and immunogenic in humans

Billeskov PLoS ONE 2012
Geldenhuys Vaccine 2015
Norrby Vaccine 2017

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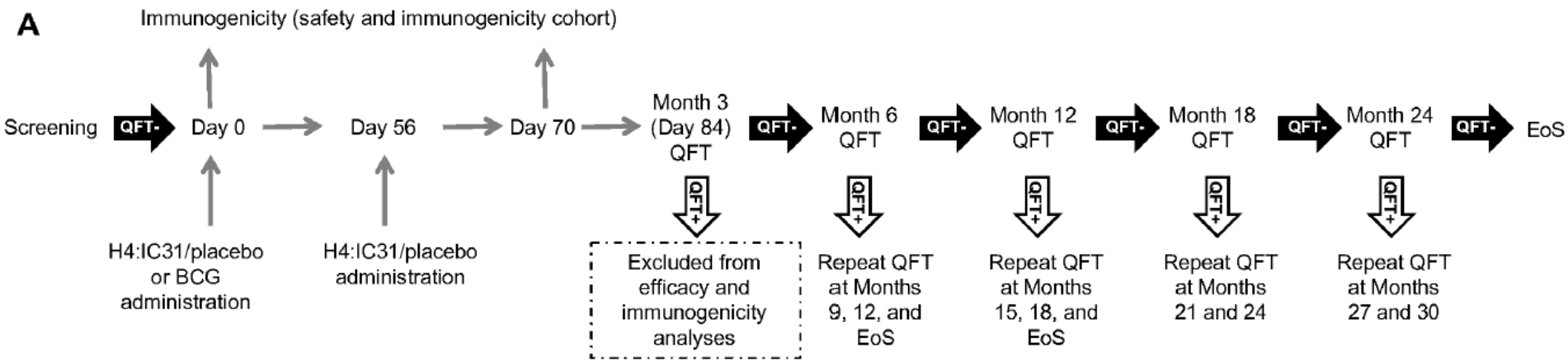
Trial Design



First cohort (n=90) additional immunogenicity

Follow-up contingent on QFT status D84 and M6, 12, 18 and 24

- QFT+ D84 'washout' period excluded
- QFT+ M6, 12, 18, 24 returned 3, 6 months later; and EoS

South African national guidelines

- Do not recommend IPT for HIV-negative *M.tb*-infected persons >5 years old (high risk of reinfection)
- Preventive therapy not provided - QFT converters

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Outcome Measures

Safety Outcomes

All participants ≥1 injection

Solicited AE 7 days, unsolicited AE and injection site AE 28 days (placebo/H4:IC31®) or 84 days (BCG), SAE and AESI to EoS

Immunogenicity Outcomes

Safety & immunogenicity cohort

Intracellular cytokine staining (ICS) and flow cytometry

Efficacy Outcomes

Analyzed mITT population, received ≥1 injection and QFT- D84

Exploratory analyses ITT and PP population

Primary efficacy endpoint:

Initial QFT conversion (IFNγ ≥0.35 IU)/mL) post-D84

Secondary efficacy endpoint:

Sustained QFT conversion through 6 months after (post-D84) QFT conversion

Exploratory efficacy endpoints:

Sustained QFT conversion through EoS

Alternative thresholds - initial/sustained QFT conversion

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Statistical Considerations

Distinguish 50% rate reduction initial QFT conversion H4:IC31® or BCG vs placebo

80% power, 10% one-sided Type 1 error rate
→ Prioritize detection proof-of-concept signal (at expense of possible False+)

Not powered to distinguish POI efficacy H4:IC31® vs BCG
Not powered to distinguish POD efficacy

Sample size (330/arm) expected → 64 initial QFT conversion endpoints

Efficacy estimates based on Hazard Ratios (Cox regression model)

Primary, secondary efficacy analyzed using log-rank tests, H4:IC31® or BCG versus placebo,

Report both –

80% confidence intervals (pre-specified significance criteria)

95% confidence intervals (traditional significance criteria)

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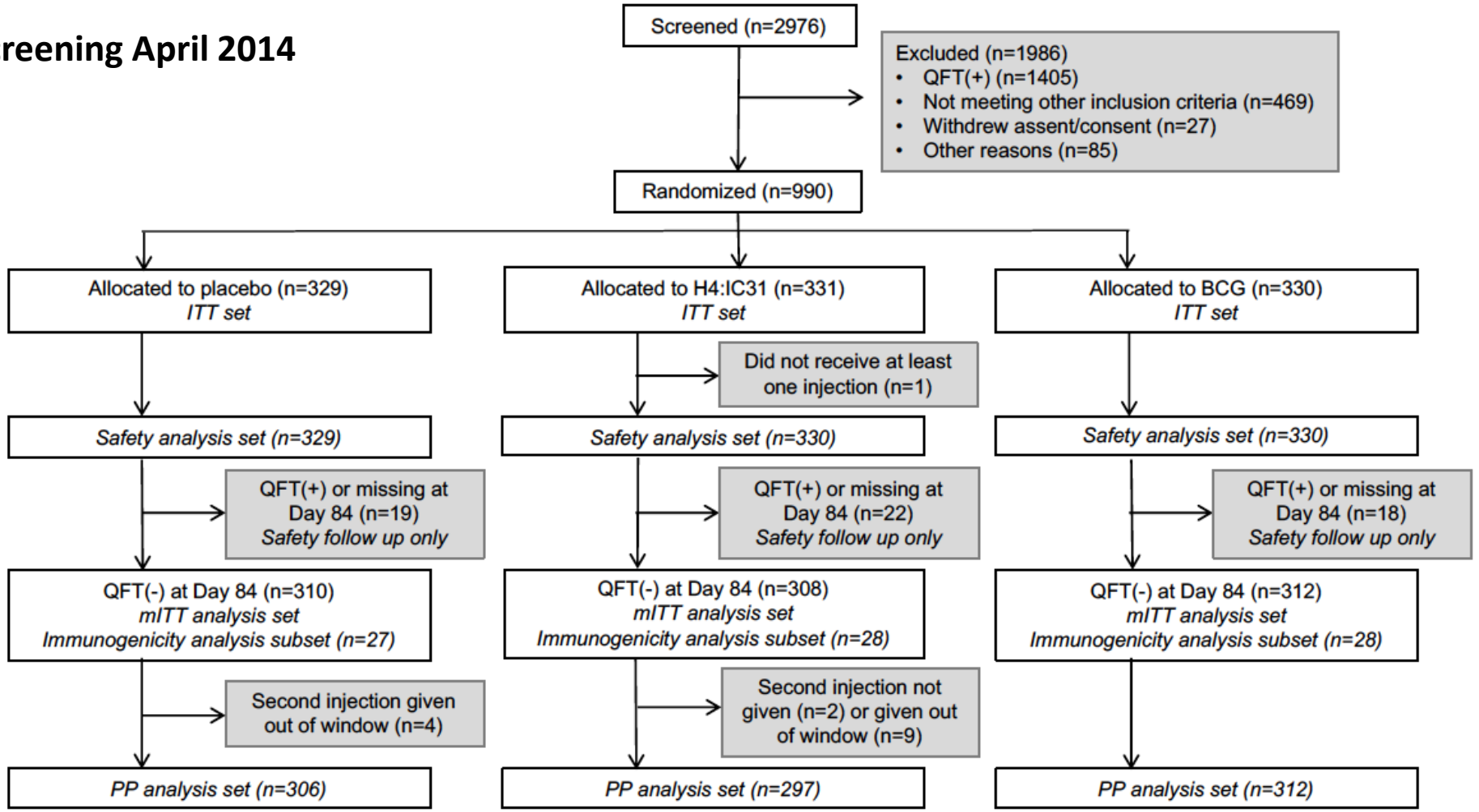
Results

Screening April 2014



LPLV August 2017

Loss to follow-up 4% (41/990) through EoS

Results: Baseline characteristics did not differ between arms

Variable		Statistic	Placebo (n=329)	H4:IC31® (n=330)	BCG (n=330)	Total (n=989)
Site	SATVI	n (%)	306 (93.0)	306 (92.7)	305 (92.4)	917 (92.7)
	DTHC	n (%)	23 (7.0)	24 (7.3)	25 (7.6)	72 (7.3)
Age (years)		Median (min, max)	14 (12, 17)	14 (12, 17)	14 (12, 17)	14 (12, 17)
Self-declared Race	Asian	n (%)	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)
	Black African	n (%)	120 (36.5)	120 (36.4)	126 (38.2)	366 (37.0)
	Caucasian	n (%)	1 (0.3)	1 (0.3)	3 (0.9)	5 (0.5)
	Cape Mixed Ancestry	n (%)	207 (62.9)	208 (63.0)	200 (60.6)	615 (62.2)
Sex (females)		n (%)	169 (51.4)	189 (57.3)	162 (49.1)	520 (52.6)
Body mass index (kg/m^2)		Median (min, max)	19.9 (14.3, 36.8)	19.6 (13.8, 38.3)	19.4 (13.1, 36.9)	19.6 (13.1, 38.3)

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Results: Safety

Both vaccines - acceptable safety profile

550 participants ≥1 AE

H4:IC31® and placebo similar AE profile

AE more frequent BCG arm (injection site AE, mild-moderate severity)

Upper respiratory tract infection less frequent BCG vs placebo and H4:IC31 (2.1%, 7.9%, and 9.4%, respectively; $p<0.001$)

In total:

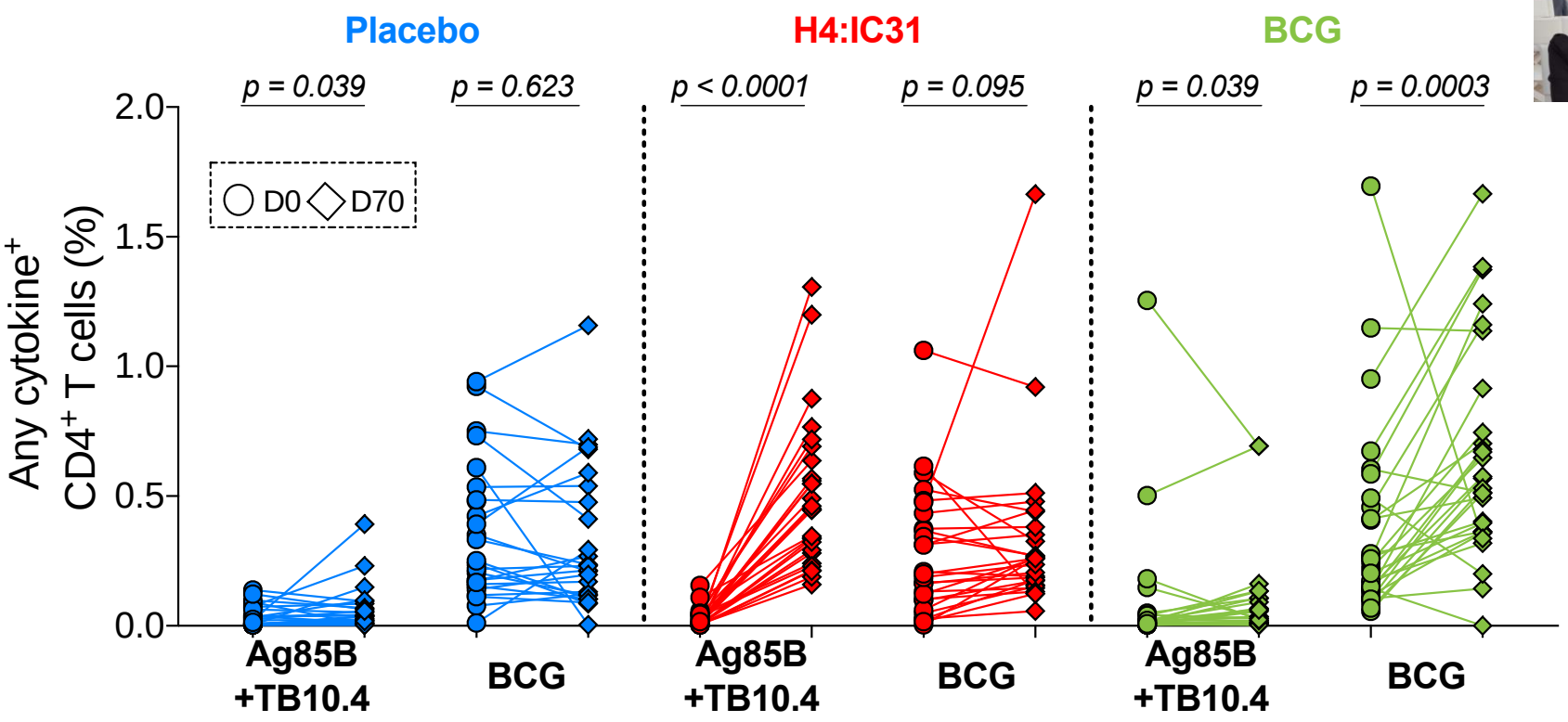
4 severe AE, 19 SAE
No AESI or related severe AE or related SAE
1 death (suicide; placebo arm)

No difference in rate of severe AE or SAE between study arms

No cases of active TB disease were observed

Results: Immunogenicity

PD34
Virginie Rozot



High baseline BCG responses
Both H4:IC31 and BCG were immunogenic

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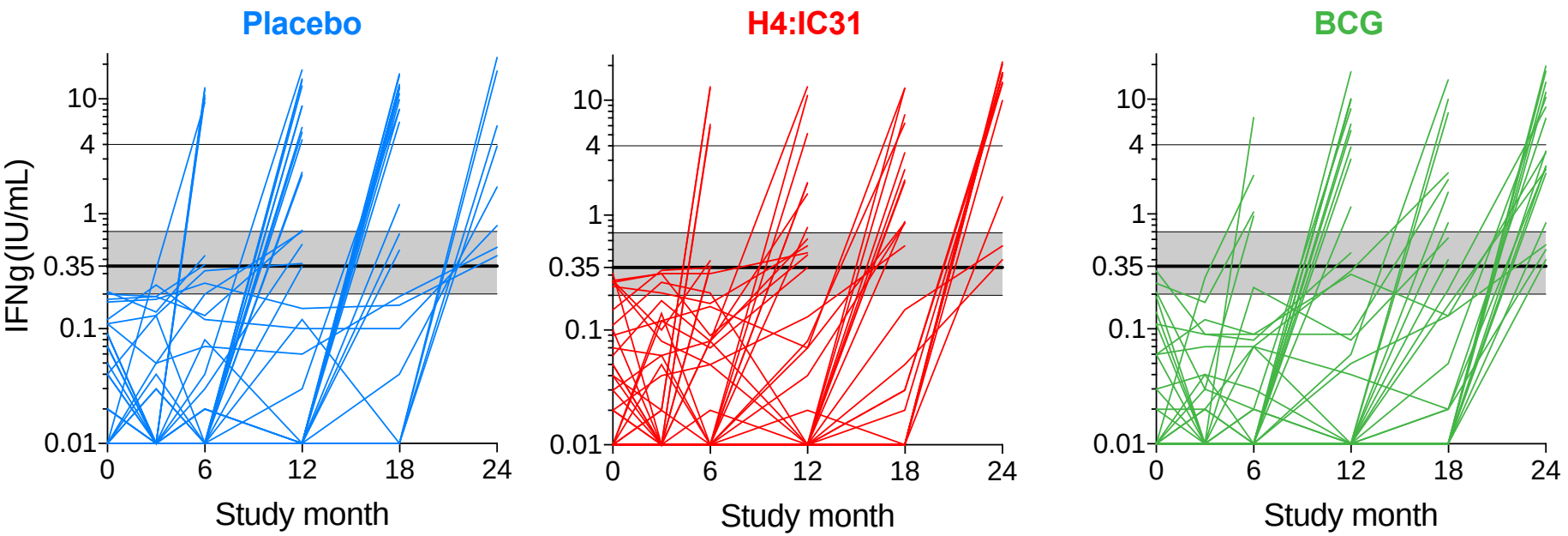
Results: Primary efficacy endpoint: Initial QFT Conversion

Total 134 initial QFT conversions (14.4%) = incidence 9.9 per 100 person-years

Placebo 15.8%

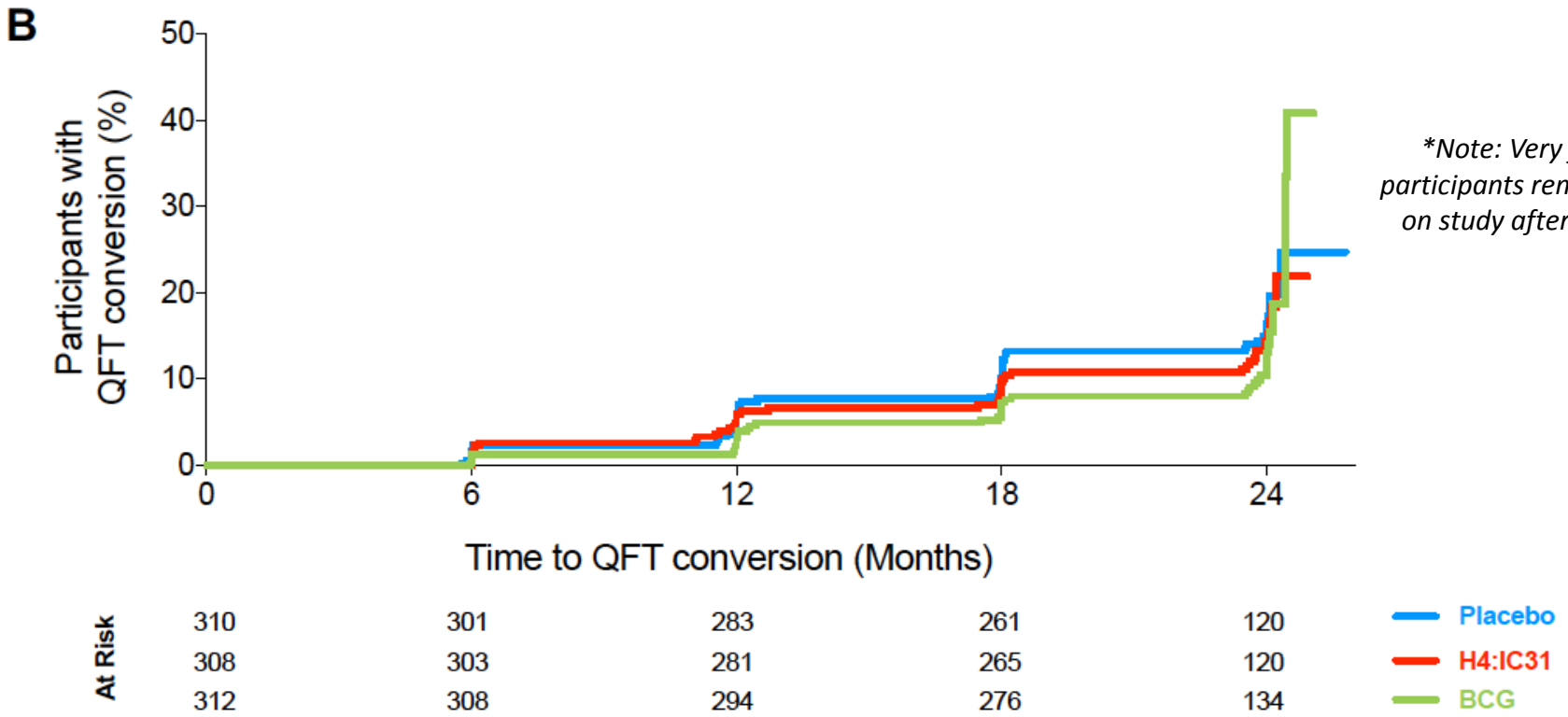
H4:IC31 14.3%

BCG 13.1%



Results: Primary efficacy endpoint: Initial QFT Conversion

Placebo	15.8%			
H4:IC31	14.3%	**VE 9.4%**	(80% CI -18.3; 30.6)	(95% CI -36.2; 39.7)
BCG	13.1%	**VE 20.1%**	(80% CI -4.8; 39.1)	(95% CI -21.0; 47.2)



**Note: Very few participants remaining on study after M24*

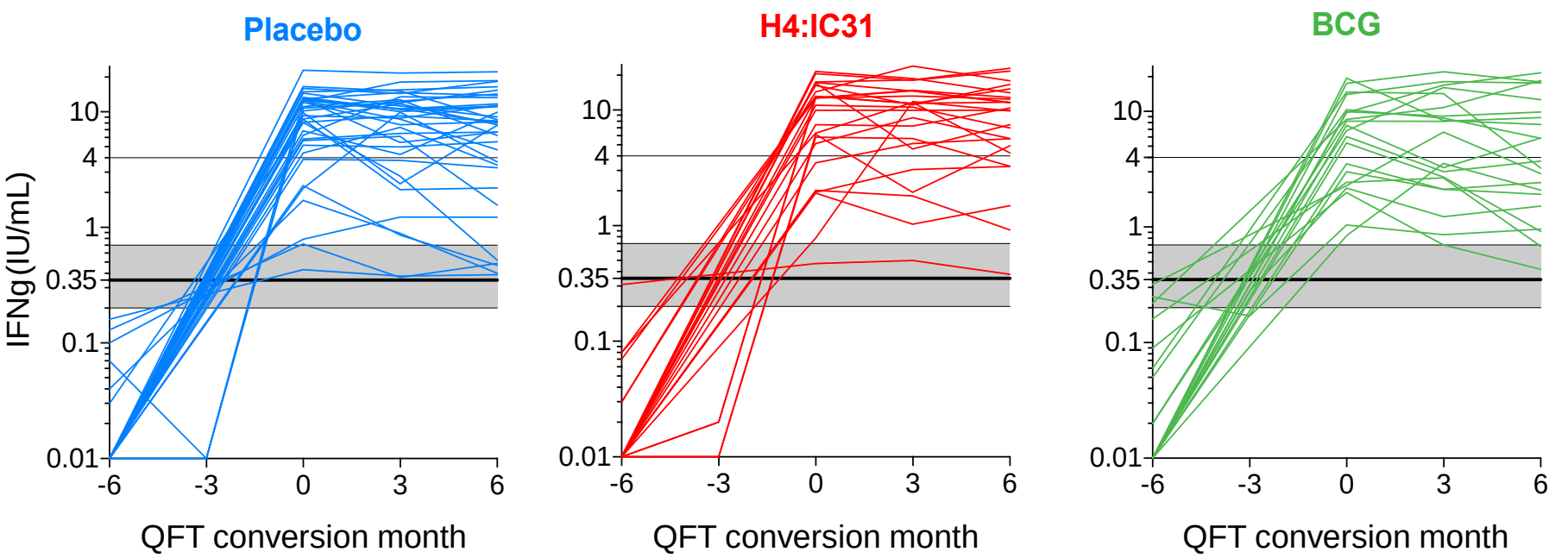
Results: Secondary Efficacy Endpoint: Sustained QFT Conversion

82 sustained QFT converters (8.8% of all participants; 62.6% of initial QFT converters)

Placebo 36/310 **11.6%**

H4:IC31 25/308 **8.1%**

BCG 21/312



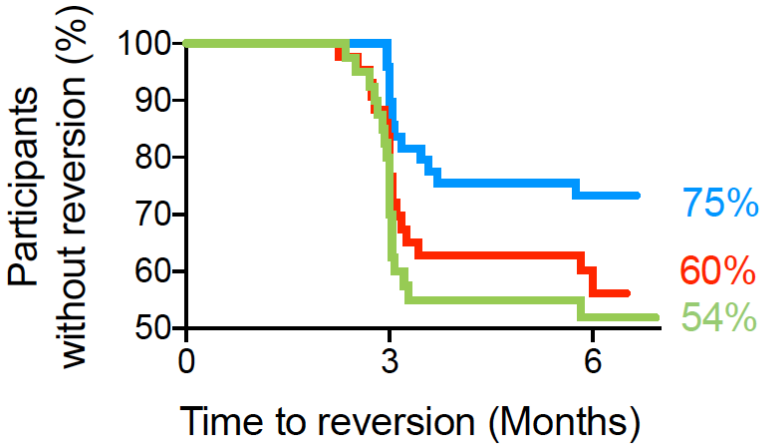
Results: QFT Reversion

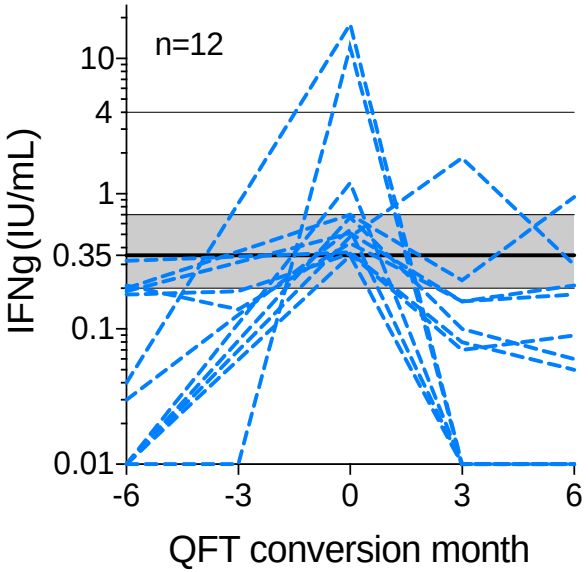
High QFT reversion rate (37.6%)

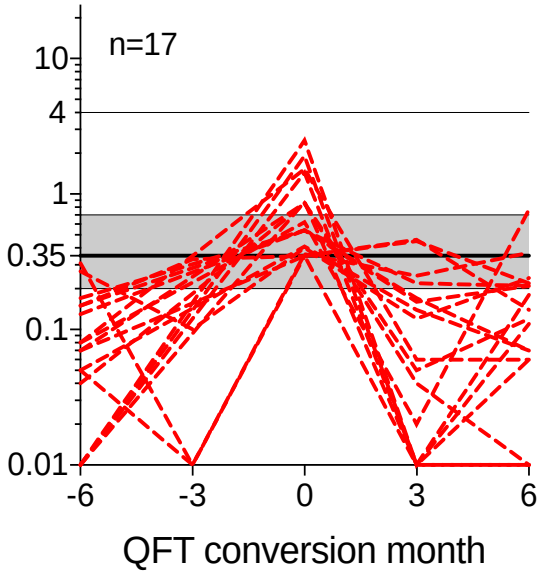
Placebo 12/48 **(25.0%)**

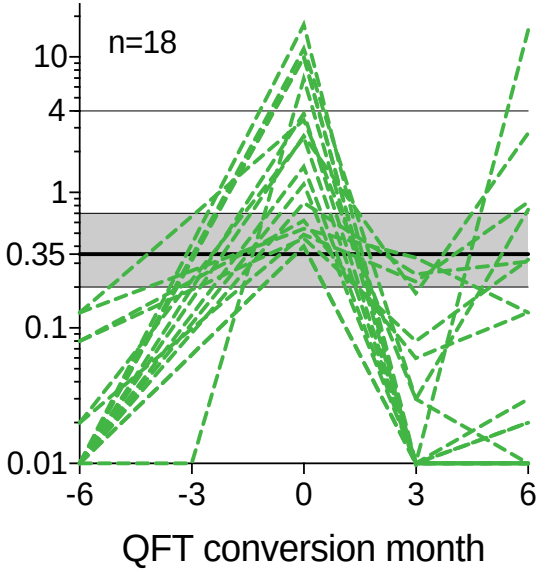
H4:IC31 17/42 **(40.5%)**

BCG 18/39 **(46.2%)**







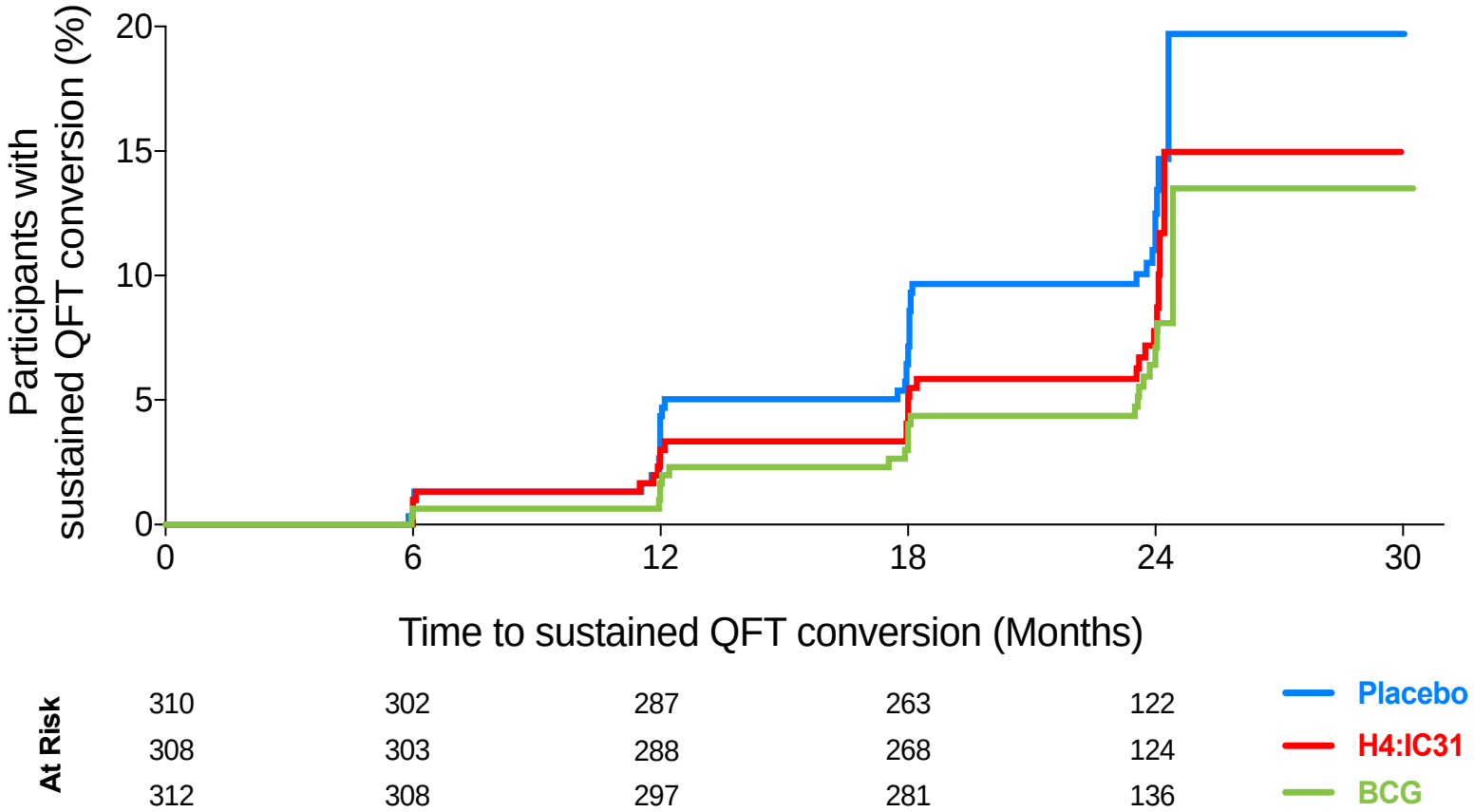


Results: Secondary efficacy endpoint: Sustained QFT Conversion

Placebo (11.6%)

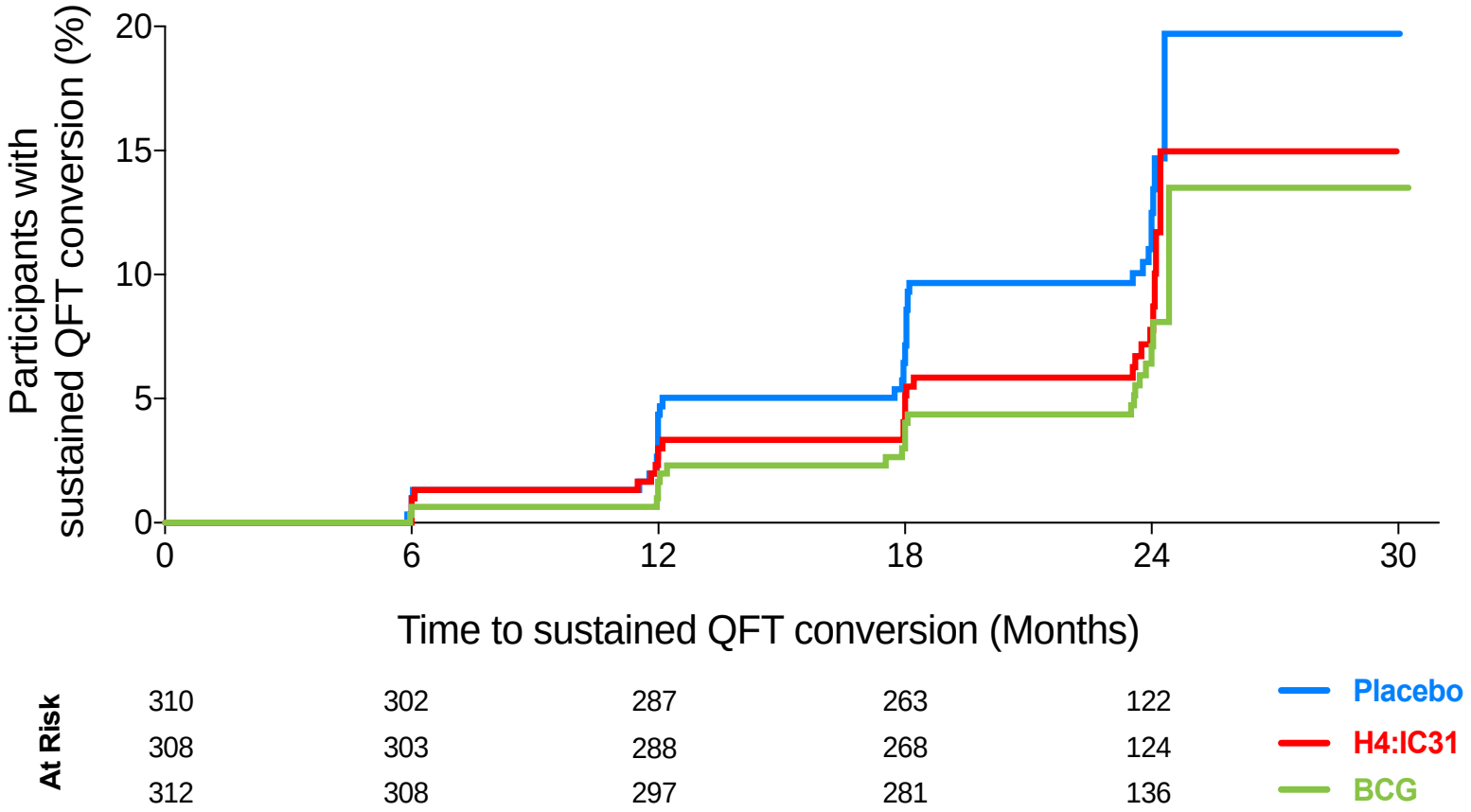
H4:IC31 (8.1%) **VE 30.5%** (80% CI 3.0; 50.2)

BCG (6.7%) **VE 45.4%** (80% CI 22.3; 61.6)



Results: Secondary efficacy endpoint: Sustained QFT Conversion

Placebo	(11.6%)			
H4:IC31	(8.1%)	**VE 30.5%**	(80% CI 3.0; 50.2)	(95% CI -15.8; 58.3)
BCG	(6.7%)	**VE 45.4%**	(80% CI 22.3; 61.6)	(95% CI 6.4; 68.1)



Results: Exploratory efficacy endpoints

PD28
Elisa Nemes

Sustained QFT conversion EoS			**(≥0.35IU/mL)**	
Placebo	11.6%			
H4:IC31	7.8%	**VE 34.2%**	(80% CI 7.7; 53.0)	(95% CI -10.4; 60.7)
BCG	6.4%	**VE 48.2%**	(80% CI 25.9; 63.8)	(95%CI 10.5; 70.0)

Sustained QFT conversion			**(<0.2 to >0.7IU/mL)**	
Placebo	10.0%			
H4:IC31	7.8%	**VE 23.2%**	(80% CI -8.8; 45.8)	(95% CI -30.9; 54.9)
BCG	6.1%	**VE 41.6%**	(80% CI 15.2; 59.8)	(95% CI -3.3; 67.0)

Initial QFT conversion			**(>4IU/mL)**	
Placebo	10.6%			
H4:IC31	7.1%	**VE 34.5%**	(80% CI 6.8; 54.2)	(95% CI -12.1; 62.3)
BCG	6.1%	**VE 45.1%**	(80% CI 20.5; 62.2)	(95% CI 3.8; 69.3)

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Summary 1

Both H4:IC31 and BCG safe and immunogenic

Neither H4:IC31® nor BCG revaccination prevented initial QFT conversion

Vaccination can reduce rate of sustained QFT conversion in high TB transmission setting

Secondary endpoint: Sustained QFT conversion

Modest signal H4:IC31® (VE 30.5%; 80% confidence 3 – 50%)

- met pre-defined significance criteria for POI proof-of-concept
- did not meet conventional criteria for statistical significance

Convincing efficacy signal BCG (VE 45.4%; 95% confidence 6 – 68%)

- met traditional significance criteria for Phase 2b trials

Summary 2

Possible explanations consistent with the results

1) No reduction in rate initial QFT conversion (primary endpoint)

- vaccination did not avert initial colonization, or antigen trafficking to lymphoid tissues to trigger adaptive immunity

2) Reduction in rate initial QFT conversion >4 IU/mL (exploratory endpoint)

- vaccine-mediated reduction in bacterial replication following initial infection

3) Reduction in rate sustained QFT conversion (secondary endpoint)

- vaccine-mediated QFT reversion associated with enhanced bacterial control or even clearance

Billeskov Plos one 2012

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Summary 3

Impact and next steps…

1) Evidence POI design can detect vaccine efficacy in high M.tb transmission setting

- identified sustained QFT conversion as suitable endpoint
- cannot confirm utility of initial QFT conversion*
- POI needs validation as tool for vaccine up-selection in future POD trial

2) Modest H4:IC31 signal, suggests biological effect

- first indication of protection against *M.tb* in humans by novel subunit vaccine
- impetus for development of related subunit vaccines

3) *Convincing BCG efficacy signal*

- allow search for immune correlates of protection
- justifies (re)evaluation of BCG revaccination for POD in *M.tb*-uninfected persons

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** ≥0.35IU/mL threshold*

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The C-040-404 Study Team

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1South African Tuberculosis Vaccine Initiative; 2Aeras; 3Statistical Center for HIV Research; 4The Desmond Tutu HIV Centre; 5Sanofi Pasteur; 6Statens Serum Institut; 7Aeras Global TB Vaccine Foundation; 8Aeras South Africa Endpoint Assay Laboratory; 9Sanofi Pasteur

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