#P35

IMPAACT P1113/Aeras C-015-404: Phase I/II Study of H4:IC31 in BCG-Primed Infants

NCT01861730

S. Nachman[1], E. Andersen-Nissen[2,3], A. Fiore-Gartland[3], J. Hural[3], M.J. McElrath[3], Z. Shi[4], J. Eisner[4], A. Coletti [5], O. Dintwe[2], C. DiazGranados [6], P. Jean-Philippe[8], M. Cotton[9], L. Fairlie[10], A. Violari[11], and the P1113 study team

1: SUNY Stony Brook, Stony Brook, NY, 2: Hutchinson Center Research Institute of South Africa, 3: Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, 4: Aeras, Rockville, MD 5: FHI 360, Durham, NC, 6: Sanofi Pasteur, Swiftwater, PA, 7: Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute for Child Health and Human Development, NIH, Bethesda, MD, 8: Maternal Adolescent Pediatric Research Branch, Prevention Sciences Program, Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, 9: FAMCRU, Stellenbosch University, Cape Town, South Africa, 10: Wits Reproductive Health Institute, Faculty of Health Sciences, University of the Witwatersrand, South Africa Shandukani, South Africa, 11: Perinatal HIV Research Unit, University of the Witwatersrand, Chris Hani Baragwaneth Hospital

ABSTRACT (As Submitted)

Introduction: Infants living in TB endemic areas are at high risk for TB disease despite vaccination with BCG at birth. H4:IC31 is an investigational vaccine containing H4 antigen (fusion protein of Mtb antigens 85B and TB10.4) plus Valneva's proprietary IC31® adjuvant and is being tested in an ongoing dose-escalating, age de-escalating study in healthy infants in South Africa.

Methods: BCG-primed, 84-98 day old infants with no evidence of TB, HIV infection or exposure were enrolled. Subjects received 3 serial injections (at entry, and days 42 and 98) of vaccine (15 or 50µg H4 with 500nmol IC31) or placebo (5:1 enrollment ratio). Safety was assessed through 7 days after the third injection. T cell responses were assessed by ex vivo intracellular cytokine staining (ICS) using multiparameter flow cytometry two weeks following the third injection. Pre-defined response criteria were designated for CD4+ and CD8+ T cell subsets as expression of at least 2 of 3 cytokines (IL-2, IFN-γ, or TNF-α) to either Ag85B or TB10.4.

Results: Seventy eight subjects were enrolled: 51% female, 77% Black, with mean age at enrollment of 90 days. There was one severe local vaccine-related AE leading to discontinuation of vaccination in that subject. CD4+ T-cell response rates were 77.8% for the 15µg dose (21/27; 95% CI: [59.2-89.4]), 54.8% for the 50µg dose (17/31; 95% CI: [37.8-70.8]) and 11.1% for placebo (1/9; 95% CI [2.0-43.5]). There were no CD8+ T-cell responses to either Ag85B or TB10.4.

Discussion: H4:IC31 AERAS-404 appeared well tolerated and was immunogenic in these infants. Further evaluation of this vaccine candidate in BCG primed infants is warranted.

Background and Objectives:

- Primary objectives of the study are to investigate the safety and immunogenicity of H4:IC31 in HIV-uninfected, HIV-unexposed, BCG-primed infants at 4 sites in South Africa.
- Here we present data on cohorts 4 and 5 (**Table 1**)
- For these cohorts, safety was followed through 7 days post dose 3
- For Cohorts 4 and 5, the immunogenicity endpoints were the response rate and magnitude of CD4+ and CD8+ T-cell responses as measured by a validated Intracellular Cytokine Staining (ICS) assay from Peripheral Blood Mononuclear Cells (PBMC) specimens obtained on Study Day 0 and 112, corresponding to baseline and two weeks post the third (and final) immunization, respectively.
  - Cytokine positivity for each cell is determined based on positivity for IL-2 and/or IFN-γ and/or TNF-α (i.e. any 2 of 3). Multiplicity adjustments were made to account for stimulation with 2 peptide pools
- *A 50% difference between placebo and vaccine is needed to open Cohort 6*
- As specified in the protocol, the CD4+ T-cell response rate together with the safety data will inform the "Go/No-go" decision for selection of the immunization dose, and opening Cohort 6.

Table 1: **Vaccine schedule and doses administered**

Cohort	Day of Vaccination	# of Doses	Treatment Regimen (H4:IC31 dose/Placebo)	Planned/ enrolled Number of subjects
4	Study Day 0, 42, 98	3	15 µg H4/500 nmol IC31	30/32
			Placebo	6/6
5	Study Day 0, 42, 98	3	50 µg H4/500 nmol IC31	30/33
			Placebo	6/7
Total				72/78

RESULTS:

Table 2: Patient characteristics

	Cohort 4 N=38	Cohort 5 N=40
Age in days, mean (SD)	90 (4.15)	91.5 (4.68)
Race: Black, N (%)	30 (78.9)	30 (75)
Female, N (%)	16 (42.1)	24 (60)
Weight (kg), mean (SD)	6.1 (0.89)	6.02 (.73)
Received Dose #2, N (%)	35 (92)	38 (95)
Received Dose #3, N (%)	32(84)	27 (67)

Blinded Safety Results (5/2016):

- One SIDS event (day 34 post dose 2) and one severe anemia event in Cohort 4
  - Six SAEs (across all cohorts, N=166 subjects): all unrelated & no trends observed
- No allergic events reported
- Vast majority of injection sites reaction have been mild (Table 3)

Table 3: Solicited AEs: Injection site reactions

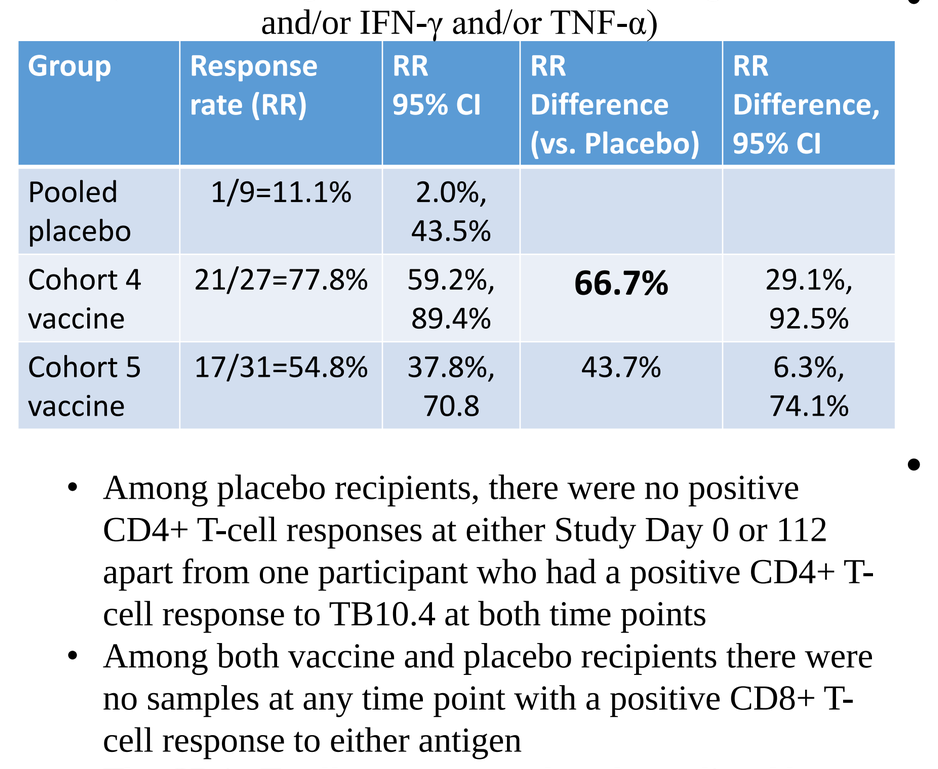
	Grade 2	Grade 3 or 4
Cohort 4, N=38	7 (18%)	0
Cohort 5, N=40	7 (17%)	1 (2.5%)

Immunogenicity:

Table 4: CD4+ T-cell response rates to at least one peptide pool (TB10.4 or Ag85B) on Study Day 112 (cells secreting at least two of the following: IL-2 and/or IFN-γ and/or TNF-α)

Group	Response rate (RR)	RR 95% CI	RR Difference (vs. Placebo)	RR Difference, 95% CI
Pooled placebo	1/9=11.1%	2.0%, 43.5%		
Cohort 4 vaccine	21/27=77.8%	59.2%, 89.4%	**66.7%**	29.1%, 92.5%
Cohort 5 vaccine	17/31=54.8%	37.8%, 70.8	43.7%	6.3%, 74.1%

- Among placebo recipients, there were no positive CD4+ T-cell responses at either Study Day 0 or 112 apart from one participant who had a positive CD4+ T-cell response to TB10.4 at both time points
- Among both vaccine and placebo recipients there were no samples at any time point with a positive CD8+ T-cell response to either antigen
- The CD4+ T-cell response was largely mediated by CD4+ T-cells expressing TNF-a and IL2



- **Figure 1**: ICS CD4+ T-cell response magnitudes to the Ag85B and TB10.4 peptide pools at study day 112.
- Combined responses to Ag85B and TB10.4 peptide pools are shown. The mid-line of the box denotes the median.
- Positivity is based on the expression of at least two of the following three cytokines: IL-2, IFN-γ and TNF-α.
- Each symbol represents a positive (red circle) or negative (blue triangle) responder.
- Overall response rates are indicated above each box plot

Figure 2: **CD4+ responses toAg85B, for Cohort 4 and 5**

*Positive response = any 2 of 3 cytokines

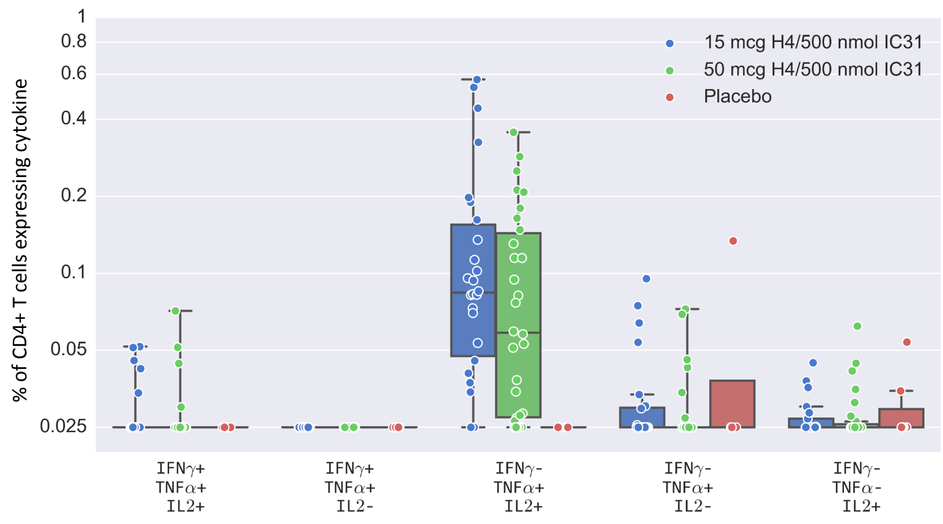


Figure 2: Polyfunctionality of CD4+ T-cell responses at day 112 to the Ag85B and 10.4 peptide pools.

- Response magnitudes for subsets of cytokine-expressing cells in each vaccine group are shown

DISCUSSION:

Safety:

- There were few safety events in Cohorts 4 and 5; blinded safety profile observed to date in study indicates an acceptable safety profile for the investigational product
  - The 6 SAEs, across all cohorts, including one SIDS were unrelated to study vaccine
- The majority of injection site reactions were mild

Immunogenicity:

- The H4:IC31 vaccine induced CD4+ T-cell responses in 77.8% of participants in cohort 4 but only 54.8% in cohort 5, compared to 11% in the placebo arm
  - *Meeting criteria for a 50% difference between placebo and vaccine in Cohort 4*
- There were few CD8+T cell responses to the vaccine antigen

CONCLUSIONS:

- Both vaccine doses were safe and well tolerated.
- The response in Cohort 4 exceeded the immunogenicity criteria allowing enrollment of a subsequent cohort; Cohort 6 will include a regimen of three immunizations coincident with EPI vaccines.
- This data supports the vaccine dose choice for cohort 6 of **15 µg H4/500 nmol IC31**
- Further evaluation of this vaccine candidate in BCG primed infants is underway.
- ***The study team thanks all the families participating in this study***.

This project has been funded in whole or in part with Federal funds from the National Institute of Allergies and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272200800014C and UM1 AI068618 6

Disclaimers: The views expressed in written conference materials or publications and by speakers and moderators at HHS-sponsored conferences, do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government