

Safety and efficacy of a trivalent P2-VP8 parenteral rotavirus vaccine candidate in healthy infants residing in Ghana, Malawi and Zambia

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Trivalent P2-VP8 Phase 3 Efficacy Study

Study title: A Phase 3 double-blind, randomized, active comparator-controlled, group-sequential, multinational trial to assess the safety, immunogenicity and efficacy of a trivalent rotavirus P2-VP8 subunit vaccine in prevention of severe rotavirus gastroenteritis in healthy infants

Sponsor: PATH

Funder: Gates Foundation

Manufacturer: SK bioscience, South Korea

Clinical sites:

- Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana
- Malawi-Liverpool-Wellcome (MLW) Programme, Blantyre, Malawi
- Centre for Infectious Disease Research in Zambia (CIDRZ), Lusaka, Zambia

Primary Objectives and Endpoints

Primary objectives:

- To assess the **relative efficacy** in prevention of **severe rotavirus gastroenteritis (SRVGE)** of the trivalent P2-VP8 vaccine candidate in comparison to ROTARIX®
- To evaluate the **safety** of the trivalent P2-VP8 vaccine candidate in healthy infants and compare with that of ROTARIX

Primary endpoints:

- Laboratory confirmed cases of **SRVGE (any strain)**
- **Serious adverse events (SAEs)**, including intussusception, through 28 days after the last dose of study vaccine
- **AEs \geq grade 2** through 28 days after the last dose of study vaccine

Secondary Objectives

Efficacy

- To assess the relative efficacy in prevention of SRVGE in the first two years of life, and in first and second year of life, separately
- To assess the relative efficacy in prevention of **very SRVGE** (VSRVGE)
- To assess the **P-type specific relative efficacy** in prevention of SRVGE and VSRVGE, for P[4], P[6], and P[8] strains
- To assess the relative efficacy in prevention of **rotavirus gastroenteritis (RVGE)** of any severity
- To assess the relative efficacy in prevention of **hospitalization** due to RVGE of any severity

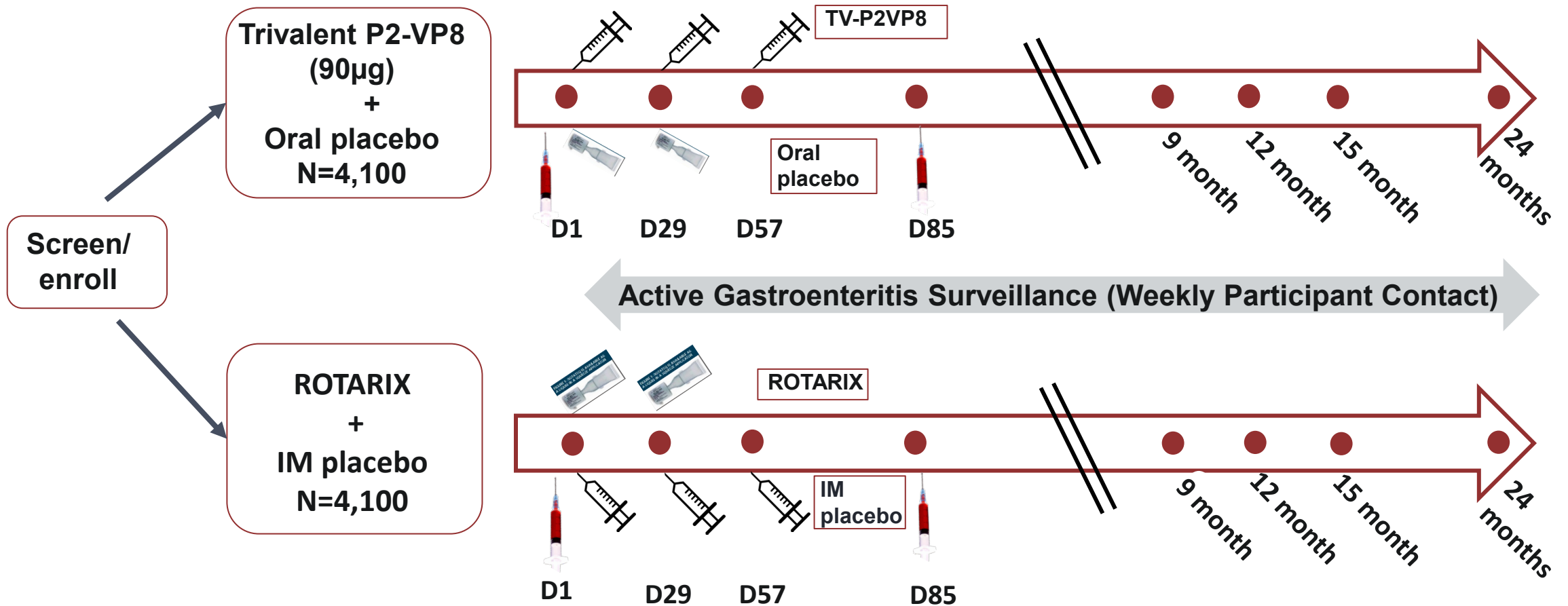
Safety

- To evaluate the tolerability (**reactogenicity**) of the trivalent P2-VP8 subunit vaccine candidate (in the week following each vaccination) and compare with that of ROTARIX
- To evaluate **longer-term safety** of the trivalent P2-VP8 vaccine candidate in healthy infants and compare with that of ROTARIX

Immunogenicity

- To evaluate the immunogenicity of the trivalent P2-VP8 vaccine candidate
- To evaluate the immune response to ROTARIX

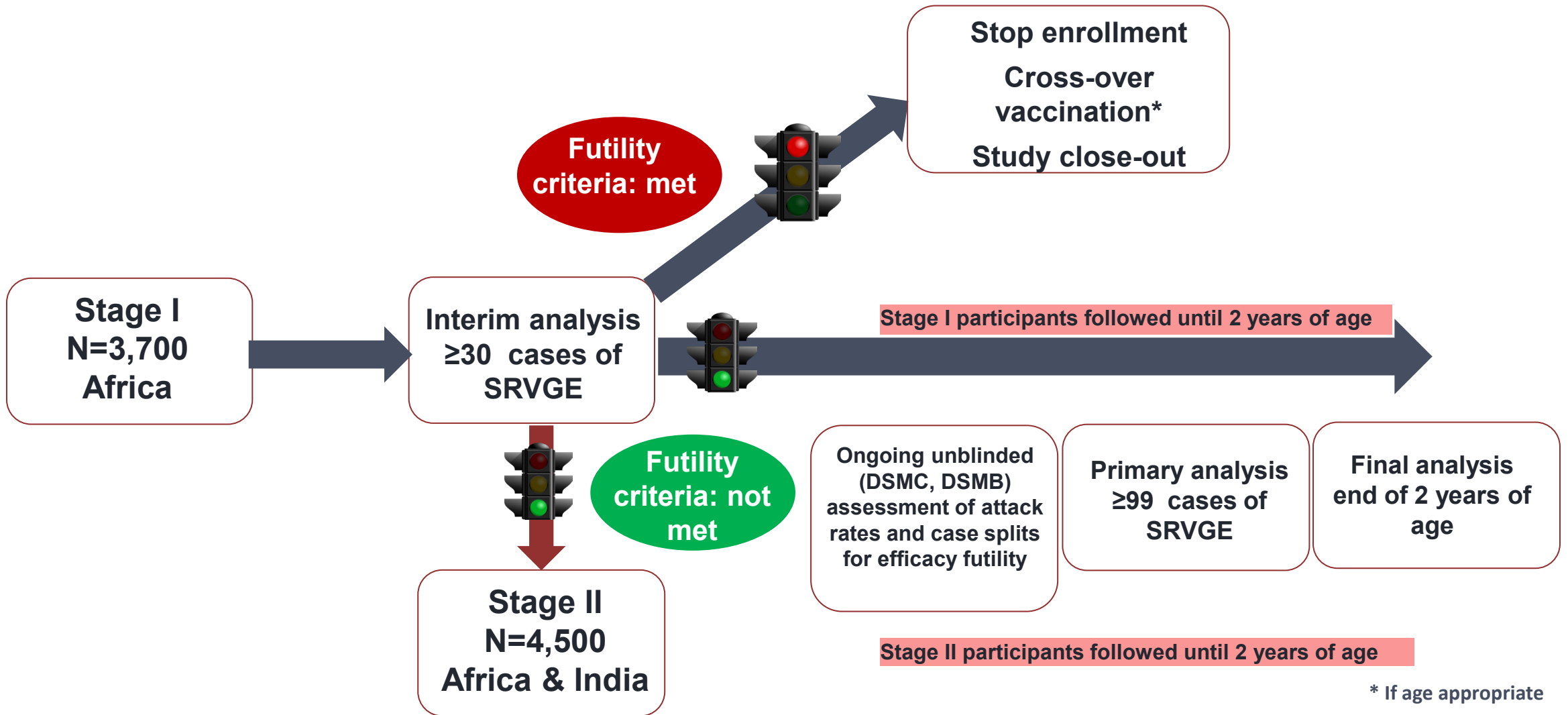
Double-Dummy Study Design



First dose at 6-8 weeks of age; subsequent doses 4 weeks (28 days) later from previous dose

Oral placebo: ORS; IM placebo: Normal saline

Group Sequential, Futility Study Design



* If age appropriate

Interim Analysis Results



Futility Criteria at Interim Analysis

Number of events analyzed at interim analysis	Number in trivalent P2-VP8 arm, resulting in futility declaration
30	≥ 16
36	≥ 19

Futility criteria met at interim analysis → Study proceeded to close-out

Details	Trivalent P2-VP8	ROTARIX	Total
Number of participants with SRVGE episodes occurring ≥14 days after third vaccination (PP)	22	14	36
Number of participants with SRVGE episodes (ITT)	27	15	42

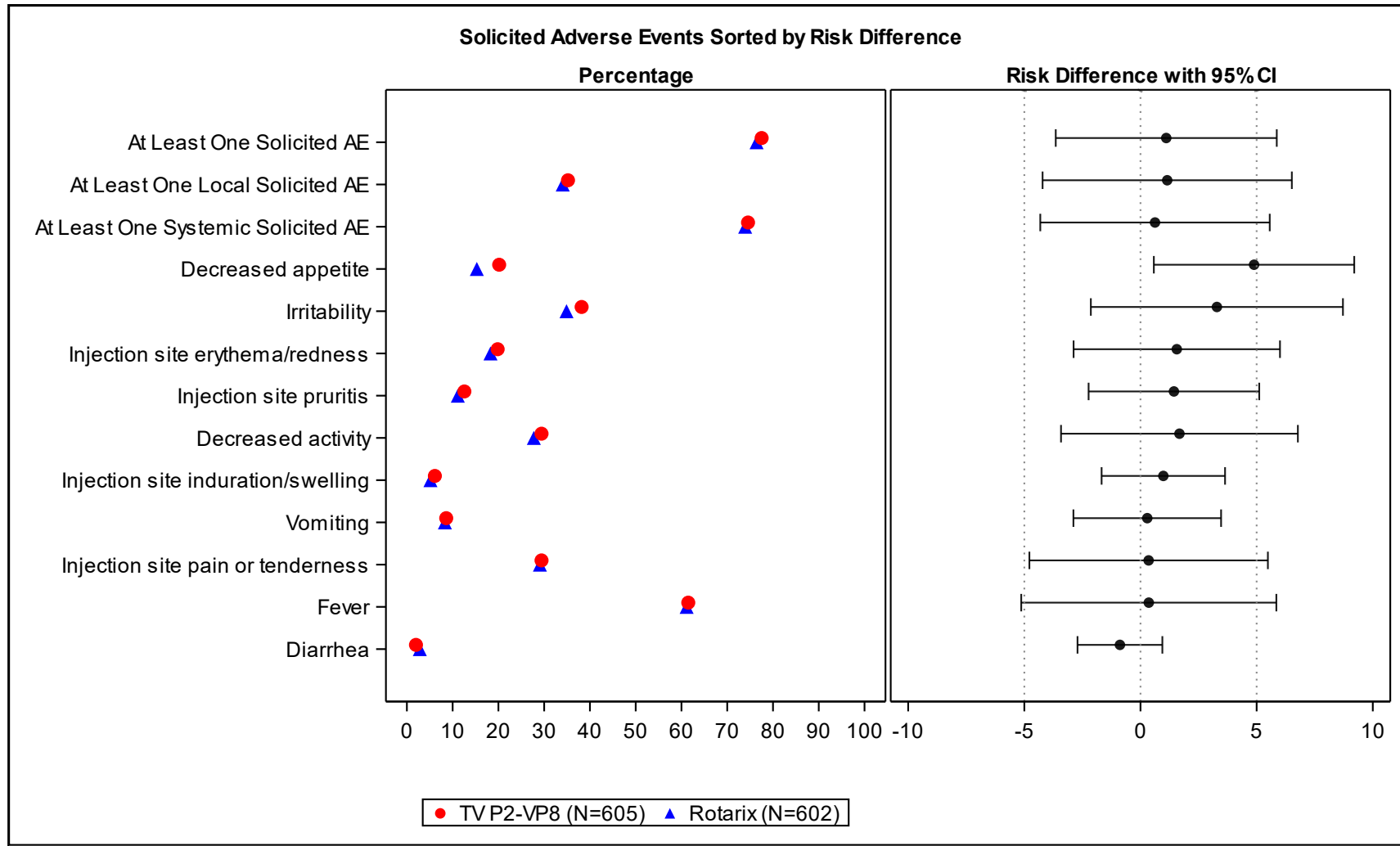
Per-Protocol Efficacy Population (PP-EFF): All participants who received all three doses of assigned study vaccines, have at least one follow-up contact/visit occurring 14 days after the third vaccine dose to assess whether the participant has experienced an episode of GE (and, if so, has provided a stool sample for RV testing), and have no major protocol deviations that are determined to potentially interfere with the efficacy assessment of the study vaccine.

Intent-to-treat Efficacy Population (ITT-EFF): All participants in the enrolled population who were randomized and have at least one post-vaccination follow-up contact/visit to assess whether the participant has experienced an episode of GE (and, if so, has provided a stool sample for RV testing).

Final Analysis: Safety Results



Risk Difference Plot Comparing Percentage of Solicited AEs



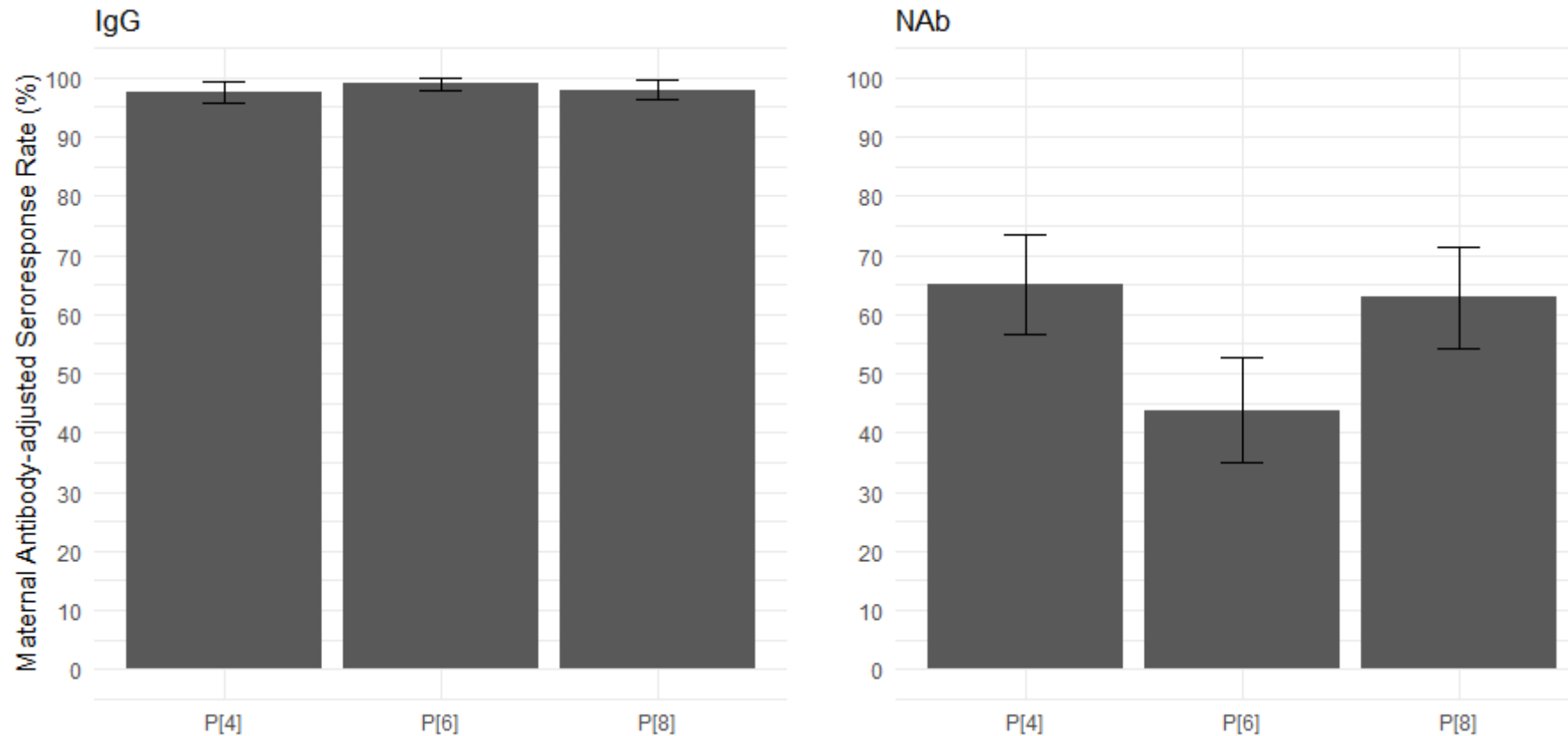
- **Trivalent P2-VP8 was safe and well tolerated.**
- Incidence rates were **generally comparable** for:
 - ✓ Immediate AEs.
 - ✓ Solicited AEs.
 - ✓ Unsolicited AEs.
 - ✓ SAEs.
- **No meaningful difference** in vitals and physical examinations.

Risk difference is computed as trivalent P2-VP8 minus ROTARIX.

Final Analysis: Immunogenicity Results

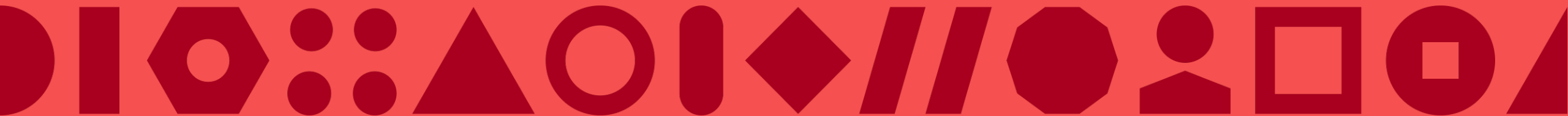


Maternal Antibody-Adjusted IgG and Neutralizing Antibody (NAb) Seropositivity Rates



- Robust serum IgG binding antibody seroconversion rates
- Neutralizing antibody seroconversion rates relatively lower

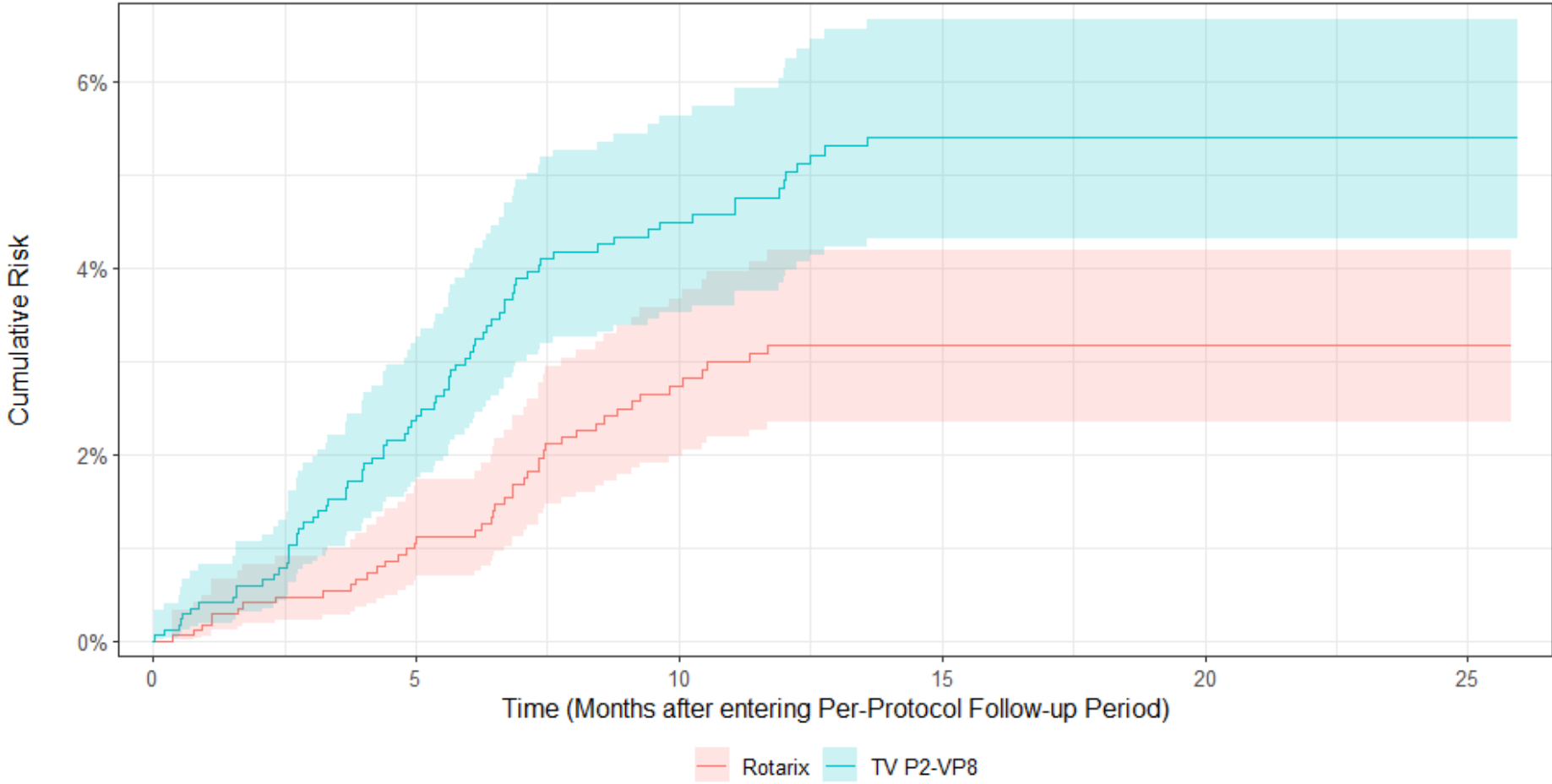
Final Analysis: Efficacy Results



Final Analysis: Laboratory-Confirmed Rotavirus

Details	Trivalent P2-VP8	ROTARIX	Total
PP-EFF population (N)	1,728	1,749	3,477
Total number of GE episodes (E)	854	845	1,699
Number of participants with RVGE episodes n(%)			
1 or more episodes	163 (9.4)	113 (6.5)	276 (7.9)
2 or more episodes	3 (0.2)	4 (0.2)	7 (0.2)
Participants with severe GEs \geq 14 days after third vaccination n(%)	146 (8.4)	132 (7.5)	278 (8.0)
Number of participants with SRVGE episodes occurring \geq 14 days after third vaccination (PP)			
1 or more episodes	78 (4.5)	45 (2.6)	123 (3.5)
2 or more episodes	1 (0.1)	0 (0.1)	1 (0.0)
Number of participants with VSRVGE episodes	30 (1.7)	12 (0.7)	42 (1.2)

Cumulative Incidence Rate of SRVGE Cases Over Time by Study Arms



The cumulative risk was higher in the trivalent P2-VP8 arm as compared to ROTARIX throughout the follow-up period.

Relative Vaccine Efficacy (RVE) in Prevention of SRVGE

Details	Trivalent P2-VP8	95% CI
RVE (%) ≥14 days post-third vaccination (PP-EFF)	-77.9	(-162.38,-21.54)
Malawi	-70.2	(-217.64,6.47)
Zambia	-77.0	(-210.35,-3.09)
Ghana	-136.4	(-1339.23,45.18)
RVE (%) until 9 months of age	-131.1	(-336.68,-28.00)
RVE (%) until 12 months of age	-91.7	(-199.20,-24.35)
RVE (%) until 18 months of age	-76.8	(-161.38,-21.07)
RVE (%) between 12-24 months of age	-31.9	(-220.37,44.49)
RVE (%) ≥14 days post-third vaccination (ITT-EFF)	-71.3	(-148.82,-19.59)

Trivalent P2-VP8 was **inferior** to ROTARIX in prevention of SRVGE during the first two years of life.

Relative Vaccine Efficacy (RVE): Secondary Endpoints

Details	Trivalent P2-VP8	95% CI
RVE (%) against VSRVGE	-155.0	(-449.44,-27.37)
RVE (%) against RVGE of any severity	-47.8	(-89.63,-15.59)
RVE (%) against SRVGE-associated hospitalization	-75.7	(-267.33,12.73)
RVE (%) against VSRVGE-associated hospitalization	-105.0	(-453.15,17.24)
RVE (%) against SRVGE by strains		
P[4]	-160.0	(-2590.36,58.06)
P[6]	-64.6	(-259.83,20.90)
P[8]	-92.2	(-206.84,-21.92)

RVE was also **negative** for all the study's secondary endpoints: VSRVGE; RVGE of any severity; hospitalization for SRVGE and SRVGE; P-type-specific SRVGE.

Overall Conclusions

- The trivalent P2-VP8 vaccine candidate provided **inferior protection** against SRVGE compared to ROTARIX in the Phase 3 study.
- The vaccine candidate was **safe, immunogenic, and well tolerated** by infants.
- Antibodies produced against the candidate **do not translate into efficacy** against SRVGE.
- Serum samples obtained from participants are undergoing further immunological analyses in an attempt to identify a correlate of risk for acquiring SRVGE.
- Scientific efforts need to continue to identify alternative rotavirus vaccine candidates with improved efficacy in low- and middle-income settings compared to the existing live, oral rotavirus vaccines.

Thank you!

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