

Project Brief: RSV_IMPACT

Full Title of Study/Programme	A Phase-IV individually randomized, placebo-controlled trial on safety of RSVA/B-preF vaccine in pregnant women and efficacy against severe RSV-associated lower respiratory tract infection in infants.
Technical Focus Area	Pregnant Women and Infants
Rationale	The pivotal phase III trial on a bivalent pre-fusogenic fusion protein (RSVA/B-preF; Abrysvo™; MATISSE trial), was undertaken in 7358 pregnant women in a multicountry, multi-centered trial. The MATISSE study included 964 (13.0%) and 196 (2.6%) enrolled from South Africa and The Gambia respectively, the only two African countries that participated in the trial (1). Furthermore, the MATISSE trial was undertaken during the COVID-19 pandemic (enrolment 17th June 2020 to 2nd October 2022). There was significant interruption of RSV circulation globally from March 2020 to December 2021, due to non-pharmacological interventions aimed at limiting transmission of SARS-CoV-2. In addition to lower rates of RSV infection than anticipated during the first year of the COVID-19 pandemic, there was also an interruption in the seasonality of RSV compared with the pre-pandemic period. Consequently, the attack rate of medically-attended LRTI (MA-LRTI) due to RSV observed through to six months of age in infants born to women who were randomized to the placebo arm (3.4%) in the MATISSE trial was lower than the same outcome in an earlier trial of a nanoparticle RSV F-protein vaccine developed by Novavax (4.6%)(2). Vaccine efficacy was observed through to six months of age for RSVA/B-preF and RSV-preF3 (another RSV prefusogenic F protein vaccine developed by GlaxoSmithKline, GSK) against RSV-confirmed MA-LRTI (51.3%; 97.58%CI: 29.4 to 66.8 and 65.0%, 95%CI: 37.5 to 82.0, respectively); as well as RSV-confirmed severeLRTI (69.4%; 97.58%CI: 44.3 to 84.1 and 69.0%, 95%CI: 33.0 to 87.6, respectively)(1,3). In the MATISSE trial, the overall rate of preterm birth was similar in the vaccine (5.6%) compared with placebo recipients (4.7%, Relative risk 1.20; 95% CI 0.98 to 1.46).

	Nevertheless, a post-hoc finding of the MATISSE trial, as well as the GSK investigational RSV-preF3 vaccine trial, reported higher rates of preterm birth in women who were randomized to receive the RSV vaccine compared with the placebo group, particularly in upper middle-income settings. In the GSK RSV-pre-F3 efficacy trial, overall higher rates of preterm delivery were observed in vaccine (6.8%) compared with placebo recipients (4.9%; Relative risk 1.37; 95%CI: 1.08 to 1.74).
Primary Objectives	i. Evaluate the efficacy of RSVA/B-preF against RSV-A or RSV-B subtype confirmed severe LRTI through to 180 days of age. The severity of LRTI will be based on the WHO grading criteria. ii. Evaluate the safety of RSVA/B-preF in relation to preterm births (born at <37 weeks GA) in women with gestational age (GA) staging Level of Certainty [LOC] 1 to 2B at time of enrolment. The GA staging will be based on Global Alignment on Immunization safety Assessment (GAIA) criteria. iii. Secondary safety objectives: Evaluate the safety of RSVA/B-preF against prematurity in women vaccinated at 28 to <32 weeks, 32 to 36 weeks, limited to women with GA staging using GAIA LOC 1 to 2B at time of enrolment. Evaluate the safety of RSVA/B-preF against prematurity occurring at 28 to <32 weeks, 32 to 36 weeks, limited to women with GA staging using GAIA LOC 1 to 2B at time of enrolment. Evaluate the safety of RSVA/B-preF against low birth weight (<2500 grams) and very low birth weight (<1500 grams).

Secondary Objectives	iv. Evaluate the efficacy of RSVA/B-preF against RSV-confirmed severe LRTI through to 90, 120 and 150 days of age. v. Evaluate the efficacy of RSVA/B-preF against RSV-confirmed LRTI resulting in (i) hospitalization and (ii) with use of supplemental oxygen OR O2 saturation of <92% (at 180 days, and 90, 120 & 150 days). vi. Evaluate the efficacy of RSVA/B-preF against RSV-confirmed MA-LRTI and very-severe LRTI (at 180 days, and 90, 120 and 150 days). vii. Evaluate the efficacy of RSVA/B-preF against RSV-confirmed: a. MA-LRTI; b. severe-LRTI; c. very-severe LRTI; d. LRTI hospitalization from 0 to 90 days and 91-180 days
Primary Endpoint/Outcome	a). Evaluating efficacy in infants who are less than 180 days during the course of the RSV season. The RSV season will be defined to have started when the positivity rate of RSV is $\geq 10\%$ (with a minimum of 10 cases being investigated in that week) for at least two consecutive weeks. The end of the RSV season will be when the RSV positivity rate is $< 10\%$ (with a minimum of 10 cases being investigated in that week) in children investigated for LRTI for two consecutive weeks after the onset of the RSV season. b) Analysis of RSV-confirmed LRTI efficacy endpoints will also be stratified in relation to whether the mothers of the infants were living with HIV (i.e. HIV-exposed infants) or without HIV (i.e. HIV-unexposed infants) during the course of the pregnancy. c) Analysis of RSV-confirmed LRTI efficacy endpoints for the composite of RSV-A or RSV-B subtype infection; as well as infections specific to RSV-A and RSV-B subtype infection.
Secondary Endpoint/Outcome	For all-cause LRTI's: vii. Evaluate the efficacy of RSVA/B-preF against all-cause: a. MA-LRTI; b. severe LRTI; c. very-severe LRTI; d. LRTI hospitalization, at 180 days, and 90, 120, and 150 days; and at 0-90 days and 91-180 days of age.

Study Design	This is a Phase IV, multicenter, randomized, double-blinded, placebo-controlled trial to assess the efficacy and safety in terms of delivery outcome of bivalent RSV A/BpreF or placebo (1:1 randomization) in infants born to women vaccinated during pregnancy. This trial aims to identify MA-LRTI cases due to RSV (meeting the case definition in the per-protocol infant population as described) and to evaluate birth outcomes. Trial-enrolment will occur year round to accommodate seasonal variation in RSV circulation, as well as investigate the efficacy of the vaccine if deployed with year-round immunization of pregnant women, rather than a seasonal approach. Trial-eligible pregnant women will be randomized in a 1:1 ratio to receive a single dose of RSV A/B-preF or placebo. For all infants born to women who receive RSV A/B-preF (infant participants), data will be collected for any medically attended respiratory illness fulfilling the LRTI definition, to evaluate for cases of severe LRTI due to RSV. Additionally, throughout the trial, all serious adverse events reported will be assessed in the trial population. Women identified as being pregnant will be contacted, informed of the trial and approached for consent for trial participation of themselves and their babies. The maternal participants will be enrolled into the trial between ≥ 28 days and < 360 days weeks gestation using GAIA assessment of gestational age in pregnant women. Enrolment will be limited to women in whom GA staging fulfills GAIA LOC criteria 1 to 2B. Prescreening and consenting for trial participation will be allowed for before 28 weeks of gestational age.
Study Arms	n/a
Study Population	The phase IV trial will be undertaken in The Gambia, Kenya (two sites), Ghana (two sites) and in South Africa (5 sites). The trial will enroll pregnant women over a period of two to three years in South Africa and two years in The Gambia, Kenya and Ghana. The live-births of the enrolled women will be followed up for at least a year after birth. Enrolment into the trial will be throughout the year. The duration of the phase IV trial is expected to be 42 months from its start in South Africa, and through to completion of follow-up of the infants until 365 days of age. Overall, a cohort of 13, 000 pregnant women will be enrolled and their live-births will be included. The trial

	will enroll between 2000 to 4000 pregnant women in each of the four countries. Enrolment will be targeted at women from ≥ 280 days weeks and < 360 days weeks of gestational age based on the GAIA GA assessment criteria (Table 1 and Figure 1). Enrolment will be limited to women in whom GA staging fulfills GAIA LOC criteria 1 to 2B.
Study Sample Size	Overall, the trial will be powered to demonstrate that RSV A/B-preF is associated with no more than a 20% increase in preterm birth rate (i.e. upper bound of 95% confidence interval ≤ 1.2) from a conservative background rate of 8% among placebo recipients (1-sided test). A 20% increase in preterm birth rates related to RSV A/B-preF vaccination was the threshold considered to be acceptable in most countries, given the benefits of RSV vaccination in protecting against RSV severe disease. The sample size required for the primary safety endpoint (13,000 with a 1:1 randomization) would be sufficient to detect an efficacy of 70% against severe RSV associated LRTI and 40% against all-cause severe LRTI in the first 6 months of life assuming background rates of severe RSV-LRTI is above 5%. Background rates of hospitalization due to RSV and all-cause LRTI were estimated based on the South African cohort enrolled in the Novavax RSV vaccine trial (2). The incidence of hospitalization due to RSV and all-cause LRTI amongst South African participants in the Novavax trial placebo arm was 6.01% and 9.89%, respectively (unpublished data)
Follow-up/Duration	365 Days
Study/Programme Sites	• MRC, The Gambia • Noguchi Memorial Institute for Medical Research • Kintampo Health research centre • Kenya Medical Research Institute, Centre for Global Health Research- Kisumu (KEMRI - CGHR) • KEMRI-Wellcome Trust Research Programme, Kilifi • Setshaba Research Centre • University of Cape Town (UCT) • Wits Reproductive Health and HIV Institute (WRHI) • Wits Vaccines & Infectious Diseases Analytics (Wits) • Wits VIDA Nkanyezi Research Unit
Intervention	The trial intervention is RSV A/B-preF (Abrysvo™). Eligible women will be randomized in a 1:1 ratio to receive

	RSVA/B-preF or placebo. The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The RSV drug product will be 120 µg of the RSV prefusion F antigen.
Operations	Study Specific
Investigators	• Dr Lee Fairlie: Principal Investigator • Dr Faeezah Patel: Sub-Investigator • Dr Elizea Horne: Sub-Investigator • Dr Mrinmayee Dhar: Sub-Investigator • Dr Jeanne Coetzee: Sub-Investigator • Tiffany Seef: Clinical Associate
Other Partners & Collaborators	n/a
Sponsors/Donors	Pfizer
Publications/Key Presentations to Date	None yet
Progress Update as of Mar 2026	Screened:473 Enrolled:320 Screen failed: 51 Withdrawals: 19 Delivered of those enrolled:166
Frequency of Donor Narrative Report	Donor reports will be sent when available and/ or as requested. Progress reports will be sent to HREC and SAHPRA biannually.
Overall Study/Project Contact	Prof. Lee Fairlie
Briefing Owner and Date	Rorisang Komane Mar 2026