Project Brief: Horizon 2

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Full Title of Study/Programme	A Randomized, Observer-blind, Phase 2/3 Adaptive Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Different Dose Levels of Ad26.COV2.S Administered as a One- or Two-dose Regimen in Healthy Adolescents From 12 to 17 Years Inclusive
Technical Focus Area	Research (Adolescent)
Rationale	This study will use young adults from VAC31518COV3001 and VAC31518COV3009 as external controls and therefore will only enroll participants who are 12 to 17 years of age
Primary Objectives	• To assess the safety and reactogenicity of Ad26.COV2.S administered IM as a 1- dose regimen (at 2.5×1010 vp per 0.25 mL, 1.25×1010 vp, and 0.625×1010 vp dose level) or as a 2-dose (56-day interval) regimen (2.5×1010 vp per 0.5 mL, 1.25×1010 vp, and 0.625×1010 vp dose levels) in adolescents. • To assess the humoral immune response of Ad26.COV2.S administered IM as a 1- dose regimen (at 2.5×1010 vp per 0.25 mL, 1.25×1010 vp, and 0.625×1010 vp dose level) or as a 2-dose (56-day interval) regimen (2.5×1010 vp per 0.5 mL, 1.25×1010 vp, and 0.625×1010 vp dose levels) in adolescents. • To assess the safety and reactogenicity of Ad26.COV2.S administered IM as a 1- dose regimen (at 2.5×1010 vp per 0.5 mL or 2.5×1010 vp per 0.25 mL, 1.25×1010 vp, and 0.625×1010 vp dose levels) or as a 2- dose (56-day interval) regimen (1.25×1010 vp, 0.625×1010 vp dose levels and at a lower, to be determined, dose level) in adolescents. • To assess the humoral immune response of Ad26.COV2.S administered IM as a 1- dose regimen (at 2.5×1010 vp per 0.5 mL or 2.5×1010 vp per 0.25 mL, 1.25×1010 vp, and 0.625×1010 vp dose levels) or as a 2- dose (56-day interval) regimen (1.25×1010 vp and 0.625×1010 vp dose

	levels and at a lower, to be determined, dose level) in adolescents. • To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 2.5×1010 vp in adolescents versus 1 dose of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3001 study (18 to 25 years of age). (If the above is demonstrated, then to demonstrate the following in sequential order) • To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 1.25×1010 vp in adolescents versus 1 dose of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3001 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 0.625×1010 vp in adolescents versus 1 dose of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3001 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 2.5×1010 vp in adolescents versus 2 doses of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3009 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 1.25×1010 vp in adolescents versus 2doses of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3009 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 1 dose of Ad26.COV2.S 0.625×1010 vp in adolescents versus 2doses of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3009 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 2 doses of Ad26.COV2.S 1.25×1010 vp in adolescents versus 1 dose of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3001 study (18 to 25 years of age). (If the above is demonstrated, then to demonstrate the following in sequential order) • NI after 2 doses of Ad26.COV2.S 0.625×1010 vp in adolescents versus 1 dose of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3001 study (18 to 25 years of age). • NI after 2 doses of Ad26.COV2.S of a lower, to be determined, dose level in adolescents versus 1

	dose of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3001 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 2 doses of Ad26.COV2.S 1.25×1010 vp in adolescents versus 2doses of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3009 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 2 doses of Ad26.COV2.S 0.625×1010 vp in adolescents versus 2doses of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3009 study (18 to 25 years of age). • To demonstrate NI of immune responses induced by 2 doses of Ad26.COV2.S of a lower, to be determined, dose level in adolescents versus 2doses of Ad26.COV2.S 5×1010 vp in young adults from VAC31518COV3009 study (18 to 25 years of age)
Secondary Objectives	• To assess the humoral immune response to 3 dose levelsa of Ad26.COV2.S (2.5×1010 vp, 1.25×1010 vp or 0.625×1010 vp) in a subset of participantsb in all study groups, at all blood collection timepoints.
Primary Endpoint/Outcome	• Solicited local and systemic AEs for 7 days post-dose 1 and 2. • Unsolicited AEs for 28 days post-dose 1 and 2. MAAEs from the first vaccination until 6 months post-dose 1 or post-dose 2. MAAEs leading to discontinuation will be collected during the entire study. • SAEs from the first vaccination until the end of the study. • AESIs from first vaccination until end of the study (incl. MIS-C). • Serological response to vaccination as measured by S-ELISA (ELISA Units/mL [EU/mL]) or equivalent assay, or VNA titers at 28days post-dose 1, and 14 days post-dose 2 • Solicited local and systemic AEs for 7 days post-dose 1 and 2. • Unsolicited AEs for 28 days post-dose 1 and 2. • MAAEs from the first vaccination until 6 months post-dose 1 or post-dose 2. MAAEs leading to discontinuation will be collected during the entire study.

	• SAEs from the first vaccination until the end of the study. • AESIs from first vaccination until end of the study (incl. MIS-C). • Serological response to vaccination as measured by VNA titers, 28days post-dose 1, and 14 days post-dose 2. • Seroresponse ratea of the VNA from baseline to 28 days post-dose 1, and 14 days post-dose 2. • For NI versus young adults from VAC31518COV3001, NI will be demonstrated in terms of humoral immune response expressed by the GMT of VNA, 28 days postdose 1 in adolescents and young adults, using an NI margin of 2/3 for the GMT ratio (GMT adolescents/GMT young adults). • NI will be demonstrated in terms of humoral immune response expressed as seroresponse rate of the VNA, 28 days after vaccination in adolescents and young adults, using an NI margin of -0.1 for the difference in seroresponse rate (seroresponse rate in adolescents minus seroresponse rate in young adults). • For NI versus young adults from VAC31518COV3009, NI will be demonstrated in terms of humoral immune response expressed by the GMT of VNA, 28 days postdose 1 in adolescents and 14 days post-dose 2 in young adults, using an NI margin of 2/3 for the GMT ratio (GMT adolescents/GMT young adults) • NI will be demonstrated in terms of humoral immune response expressed as seroresponse rate of the VNA, 28 days after vaccination in adolescents and 14 days post-dose 2 in young adults, using an NI margin of -0.1 for the difference in seroresponse rate (seroresponse rate in adolescents minus seroresponse rate in young adults). • For NI versus young adults from VAC31518COV3001, serological response to vaccination as measured by the GMT of VNA, 14 days post-dose 2 (adolescents) and 28 days post-dose 1 in young adults, using an NI margin of 2/3 for the GMT ratio (GMT adolescents/GMT young adults). • NI will be demonstrated in terms of humoral immune response expressed as seroresponse rate

	of the VNA, 14 days post-dose 2 in adolescents and 28 days post-dose 1 in young adults, using an NI margin of -0.1 for the difference in seroresponse rate (seroresponse rate in adolescents minus seroresponse rate in young adults). • For NI versus young adults from VAC31518COV3009, NI will be demonstrated in terms of humoral immune response expressed by the GMT of VNA, 14 days postdose 2 in adolescents and young adults, using an NI margin of 2/3 for the GMT ratio (GMT adolescents/GMT young adults). • NI will be demonstrated in terms of humoral immune response expressed as seroresponse rate of the VNA, 14 days post-dose 2 in adolescents and young adults, using an NI margin of -0.1 for the difference in seroresponse rate (seroresponse rate in adolescents minus seroresponse rate in young adults).
Secondary Endpoint/Outcome	• Binding antibody titers to SARS-CoV-2 or individual SARS-CoV-2 proteins (eg, S protein) as measured by ELISA (or equivalent assay), and/or • Neutralizing antibody titers to SARS-CoV-2 as measured by VNA titers.
Study Design	
Study Population	Participants will be vaccinated at the study site according to the schedules detailed below: • Three dose levels of Ad26.COV2.S will be used, 2.5×1010 vp, 1.25×1010 vp, and 0.625×1010 vp. Ad26.COV2.S will be supplied at a concentration of 1×1011 vp as a suspension in single-use vials, with an extractable volume of 0.5 mL. Formulation buffer will be supplied as diluent to prepare the 2.5×1010 vp, 1.25×1010 vp, and 0.625×1010 vp dose level. • Placebo will be supplied as a 0.9% NaCl solution. Participants allocated to the 2.5×1010 vp dose level in Part 1 and the 1-dose regimen in Part 2 will receive 1 of 2 volumes: 0.5 mL or 0.25 mL. A volume of 0.5 mL will be administered to all other dose groups in Part 1 and Part 2
Study Sample Size	In Part 1, a target of approximately 300 adolescents, seronegative for SARS-CoV-2 antibodies at baseline will be enrolled in a 2-dose regimen. In Part 2, the sample size will be between 1,250 (if 1 regimen is selected) and 3,000 (if 2 regimens are selected) adolescent participants, depending on the number of different dose regimens selected, of which 1,000 participants will be enrolled in the selected Ad26.COV2.S regimen for safety evaluation.

	The overall sample size including Part 1 and Part 2 will be between 1,550 to 3,300 adolescent participants, depending on the number of regimens selected for the Expansion Cohort (Part 2).
Follow-up/Duration	The study duration from screening until the last follow-up visit will be, excluding the 28-day screening phase, approximately: • 14-22months for Part 1, consisting of: – a 12-month study period including vaccination with a 1-dose or 2-dose (56-day interval) regimen and follow-up (safety and immunogenicity) until 12 months after the second vaccination or after the last vaccination in the additional vaccination(s) regimen. • 12-22months for Part 2, consisting of: – up to a 12-month study period including vaccination with a 1- or 2-dose (56-day interval) regimen and follow-up (safety and immunogenicity) until 12months after the last vaccination in the primary regimen, and up to 14 months for the 2-dose regimen (12 months after the second vaccination.
Study/Programme Sites	7 Sites in South Africa
Study/Programme Duration	Start Date: May/June 2022 Estimated end date: May/June 2024
Investigators	• **Prof Lee Fairlie, Principal Investigator** • **Dr Faeezah Patel** • **Dr Elizea Horne** • **Tiffany Seef** • **Othusiste Segalo** • **Dr Mrinmayee Dhar**
Other Partners & Collaborators	Janssen Vaccines & Prevention B.V
Sponsors/Donors	Janssen Vaccines & Prevention B.V
Publications/Key Presentations to Date	Not yet
Progress Update Aug 2022	Screened:51 Pre-screening:69 Enrolled:12 Consent withdrawal:00 Completed study: 12
Frequency of Donor Narrative Report	6 Monthly
Overall Study/Project Contact	Dr Hermien Gous
Briefing Owner and Date	Prof Lee Fairlie April 2022