South African Health Products
Regulatory Authority
Building A
Loftus Park
Arcadia
Pretoria

APPLICATION TO CONDUCT A CLINICAL TRIAL

Guidance in conditions of a Public Health Emergency

*** Application to conduct a clinical trial with limited information**

It is recognized that during a Public Health Emergency, new and experimental treatments may become necessary. Clinical trials are essential to provide the evidence to develop appropriate policies for patient treatments.

There may be little information available and a need for regulatory guidance. However, applications need to contain a certain minimum information to enable a meaningful evaluation and regulatory decision. Applicants should attempt to provide the information listed below and justify when this is not available.

The required information is GRADED as follows:

ESSENTIAL – Application will not be considered without this

IMPORTANT – Necessary information that must be provided later – Justify if not available

NOT ESSENTIAL – May be omitted from this preliminary application

All incomplete information should be explained, justified and provided to CTC as a complete CFT-1, when available. This may mean that repeat evaluations of an application may be necessary.

First Publication released for implementation	V1 April 2020

Study title	Open-label, single-arm phase 3B implementation study to monitor the effectiveness of the single shot Ad26.COV2.S COVID-19 vaccine among health care workers in South Africa
Protocol No.	ENSEMBLE OPEN LABEL: Sisonke (Together) - COV3001-Open Label Study
Version No.	Version 1.0, Dated 08 February 2021
Study Medicine	Ad26.COV2.S by Janssen administered as a single injection
SAHPRA*Ref. no. (if applicable)	Ad26.COV2.S is not currently registered with SAHPRA (SAHPRA ENSEMBLE VAC31518COV3001 Protocol Reference Number: 20200434)
SAHPRA*Ref number(s) of comparator medicine(s) (if applicable)	Not Applicable
SAHPRA* Ref number(s) of concomitant medicine(s) (if applicable)	Not Applicable
Date(s) SAHPRA approval of previous protocol(s)	SAHPRA ENSEMBLE VAC31518COV3001 Study Protocol Reference Number: 20200434, approved 22 September 2020
Sponsor:	South African Medical Research Council (SAMRC) STUDY PRODUCTS PROVIDED BY Janssen, Johnson & Johnson
Applicant:	South African Medical Research Council (SAMRC)
Contact Person:	Glenda Elisabeth Gray
Address:	SAMRC, Francie Van Zijl Road, Parow Valley, Cape Town PO Box 19070, Tygerberg 7505
Telephone No.:	+27 21 938 0905
Fax No.:	Not Applicable
Cell No.:	+27 83 459 2680
E-mail address:	Glenda.Gray@mrc.ac.za
Date of Application:	08 February 2021

Refers to registration number for registered medicines issued by SAHPRA

CHECK-LIST

Refer to the Appendix for instructions – UNSHADED ITEMS ARE ESSENTIAL

☒	**Cover Letter - (one signed copy in PDF and one copy in MS-WORD format)**
☒	**Cover page and fully completed application**
☒	**Two completed clinical trials application (CFT1) (one signed copy in PDF and one copy in MS-WORD format)**
☒	**Protocol – [if not finalized, must be close to finalization]**
☒	**Patient Information Leaflet(s) AND Informed Consent Form(s) – [Draft form]**
☐	**Copy/ies of Recruitment Advertisement(s) (if applicable) and Questionnaires** **Not Applicable**
☐	**Investigators' Brochure and / or all Professional Information (Package Insert(s))** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**Certificate(s) of Analysis Not Applicable** **Not Applicable**
☐	**Signed Investigator's CV(s) in SAHPRA format** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**Signed Declaration(s) by all Investigator(s)** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**Signed Joint Financial Declaration (Sponsor and National PI) [Justify if not available}** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☒	**Signed Declaration by Applicant and National Principal Investigator**
☐	**CV(s) and Signed Declaration by Regional Monitor(s) [Justify if not available}** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☒	**Proof of Application to Register the Trial on the South African National Clinical Trials Register**
☐	**Active Insurance Certificate for Clinical Trial [Justify if not available]** **Pending**
☐	**Proof of Sponsor Indemnification for Investigators and Trial Site [Justify if not available]** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**GCP Certificates** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**Workload Forms for Investigators** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**Proof of Registration with Professional Statutory Body (HPCSA, SAPC, SANC, etc)** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**
☐	**Proof of Professional Indemnity (Malpractice Insurance)** **Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application**

☐ Ethics Approval Letter or Copy of letter submitted to Ethics Committee Pending
☐ Study Budget Pending
☒ Citations
☐ Two Labelled CD-ROM (List of files submitted on CD-ROM) Not Applicable
☐ One USB flash drive Not Applicable
☒ Proof of payment EFT processed. Awaiting proof of payment by SAMRC

NB: In an Emergency of public Health importance SAHPRA may accept Research Clinical Trial applications for evaluation with reduced information together with a commitment to update and complete the require information as soon as possible

Declaration by Applicant

I/We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

I/We, the undersigned will ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.

Glenda Elisabeth Gray

_____

Print name

_____ 8th February 2021

1st Applicant (local contact) Date

Linda-Gail Bekker

_____

Print name

_____ 8 February 2021

Alternative (local contact) Date

Declaration by National Principal Investigator

I, the undersigned as National Principal Investigator agree that I have reviewed the application and protocol and will ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.

Glenda Elisabeth Gray

_____

Print name

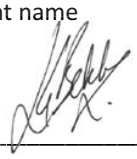
_____ 8th February 2021

National Principal Investigator Date

Linda-Gail Bekker

_____

Print name



_____ 8 February 2021

National Principal Investigator Date

SECTION 1: ADMINISTRATIVE

PART 1: ADMINISTRATIVE DETAILS	
1.1 Study Title	Open-label, single-arm phase 3B implementation study to monitor the effectiveness of the single shot Ad26.COV2.S COVID-19 vaccine among health care workers in South Africa
1.2 Protocol No, Date and Version	ENSEMBLE OPEN LABEL: Sisonke (Together) – COV3001 Open Label Study Version 1.0 Date 08 February 2021
1.3 Phase of trial	Phase 3B
1.4 Sponsor	South African Medical Research Council (SAMRC) STUDY PRODUCTS PROVIDED BY Janssen, Johnson & Johnson
1.5 Applicant	South African Medical Research Council (SAMRC)
1.6 Contact Person (Address, Telephone Number, Fax Number, E-mail Address)	Glenda Elisabeth Gray Address: SAMRC, Francie Van Zijl Road, Parow Valley, Cape Town PO Box 19070, Tygerberg 7505 e-mail: Glenda.Gray@mrc.ac.za Contact details: [redacted]27 21 938 0905
1.7 National Principal Investigator/Coordinator (or equivalent person)	Name: Glenda Elisabeth Gray Address: SAMRC, Francie Van Zijl Road, Parow Valley, Cape Town, PO Box 19070, Tygerberg 7505 e-mail: Glenda.Gray@mrc.ac.za Contact details: +27[redacted]+27 21 938 0905 Name: Linda-Gail Bekker Address: The Desmond Tutu HIV Centre, University of Cape Town, Observatory, Cape Town. e-mail: Linda-Gail.Bekker@hiv-research.org.za Contact details: +27 21 650 6970/[redacted]
1.8 International Principal Investigator (if applicable)	Not Applicable
1.9 Regional Monitor	The monitoring will be supported by the Hutchinson Clinical Research Institute of South Africa (HCRISA)

PART 2: DETAILS OF TRIALISTS AND SITES	
2.1 Details of Site(s) (Name of site, physical address, contact details, contact person)	**Site 01** Site name: PHOENIX Pharma (Pty) Ltd, Dr Daniel Rudolf Malan Physical Address: 2 Eastbourne Road, Mount Croix, Port Elizabeth, 6001, South Africa Contact Details: Tel: +27(0) 41 373 3832 Cell: [redacted] Fax: +27(0) 41 86 547 2938 E-mail: niel.malan@phoenixpharma.co.za Contact Person: Dr Daniel Rudolf Malan **Site 02** Site name: Desmond Tutu Health Foundation Clinical Trials Unit, Dr Sheetal Kassim Physical Address: J52 Old Main Building, Groote Schuur Hospital, Main Road, Observatory, 7925, Cape Town, South Africa Contact Details: Tel: +27(0) 21 406 6958 Cell: [redacted] Fax: +27(0) 21 447 1025 E-mail: Sheetal.Kassim@hiv-research.org.za Contact Person: Dr Sheetal Kassim **Site 03** Site name: TASK Central, Dr Ramonde Fiona Patientia Physical Address: 1: TASK Applied Science, Central, 1 De Lange Street, Bellville, 7530, Cape Town, South Africa Tel: +27(0) 21 917 1226 Fax: +27(0) 21 945 2083 2: TASK Clinical Research Centre, 1 Smal Street, Belville, 7530, Cape Town, South Africa Tel: +27(0) 917 1044 Fax: +27(0) 917 1046 3: TASK Aplied Science, Brooklyn Chest Hospital Premises, 1 Stanberry Road, Ysterplaat, 7405, Cape Town, South Africa Tel: +27(0) 21 510 2209 Fax: +27(0) 21 510 7108 4: TASK Applied Science, Delft Day Hospital Premises, Delft Main Road, Delft, 7100, Cape Town, South Africa Tel: +27(0) 21 954 1170 Fax: +27(0) 21 954 1165

	5: TASK Applied Science, Dr Ivans Toms Clinic Premises, c/o Nquabelani Road and Umbashe Street, Ext 6, Mfuleni, 7100, Cape Town, South Africa Tel: +27(0) 21 909 0273 Fax: +27(0) 21 909 0277 Contact Details: Tel: +27(0) 21 100 3606 Cell: +2[redacted] Fax: +27(0) 086 621 5104 E-mail: ahd@task.org.za Contact Person: Prof Andreas Diacon **Site 04** Site name: Perinatal HIV Research Unit Kliptown, Dr Erica Maxine Lazarus Physical Address: Office no. 7, Walter Sisulu Square, Corner Union and Klipspruit Valley Roads, Kliptown, Soweto, 1809 Contact Details: Tel: +27(0) 11 342 4075 Cell: [redacted] Fax: +27(0) N/A E-mail: lazaruse@phru.co.za Contact Person: Dr Erica Maxine Lazarus **Site 05** Site name: FAMCRU (Family Clinical Research Unit), Dr Shaun Lawrence Barnabas Physical Address: University of Stellenbosch, Pediatric Infectious Diseases Clinical Research Unit, Ward J8, Tygerberg Academic Hospital, Francie van Zijl Drive, Parow Valley, South Africa, 7505 Worcester Satellite Site: 1 Sugget Street, Worcester. 6850 Contact Details: Tel: +27(0) 21 938 4292 Cell: [redacted] Fax: +27(0) 21 938 5662 E-mail: barnabas@sun.ac.za Contact Person: Dr Shaun Lawrence Barnabas **Site 06** Site name: Chatsworth Clinical Research Site, Dr Logashvari Naidoo Physical Address: South Africa Medical Research Council, HIV Prevention Research Unit, R.K. Khan Circle, Chatsworth, KwaZulu Natal, South Africa, 4030 Contact Details: Tel: +27(0) 31 401 4150 Cell: [redacted] Fax: +27(0) 31 401 4563 E-mail: logashvari.naidoo@mrc.ac.za Contact Person: Dr Logashvari Naidoo

	Site 07 Site name: Josha Research, Dr Johannes Jurgens Lombaard Physical Address: 28 East Burger Street, Bloemfontein, 9300, South Africa Contact Details: Tel: +27(0) 514 128 160 Cell: [redacted] Fax: +27(0) 514 128 190 E-mail: josha.research@power4u.co.za Contact Person: Dr Johannes Jurgens Lombaard **Site 08** Site name: Setshaba Research Centre, Dr Mookho Malahleha Physical Address: 2088 Block H, Soshanguve, 0152, South Africa Contact Details: Tel: +27(0) 12 799 2422 Cell [redacted] Fax: +27(0) 12 799 2685 E-mail: MMalahleha@setshaba.org.za Contact Person: Dr Mookho Malahleha **Site 09** Site name: The Aurum Institute: Tembisa Clinical Research Centre, Dr Kathryn Therese Mngadi Physical Address: Clinic 4, cnr Rev RTJ Namane and Flint Mazibuko Drive, Hospital View, Tembisa, Gauteng, South Africa, 1632 Contact Details: Tel: [redacted] Cell: [redacted] Fax: +27(0) 86 759 2728 E-mail: kmngadi@auruminstitute.org Contact Person: Dr Kathryn Therese Mngadi **Site 10** Site name: Qhakaza Mbokodo Research Clinic, Dr Philippus Lodewicus Kotzé Physical Address: 15 Parklane, Mkhamba Gardens, Ladysmith, Kwa-Zulu Natal, South Africa, 3370 Contact Details: Tel: +27(0) 36 631 2372 Cell: [redacted] Fax: +27(0) 36 631 0021 E-mail: plkotze@gmail.com Contact Person: Dr Philippus Lodewicus Kotzé

	Site 11 Site name: The Aurum Institute Klerksdorp Clinical Research Centre, Dr James Craig Innes Physical Address: The Aurum Institute: Gavin J Churchyard Legacy Centre, Klerksdorp Clinical Research Centre, 201 Jade Square Centre, Cnr Margaretha Prinsloo and OR Tambo Drive Klerksdorp, North West Province, South Africa, 2571 Contact Details: Tel: +27(0) 87 135 1616 Cell: [redacted] Fax: +27(0) 87 231 4977 E-mail: cinnes@auruminstitute.org Contact Person: Dr James Craig Innes **Site 12** Site name: The Aurum Institute: Rustenburg Clinical Research Centre, Dr William Lawrence Brumskine Physical Address: First Floor, 50 Steen Street, Cnr Pretorius Street, Rustenburg, North West, South Africa, 0299 Contact Details: Tel: +27(0) 87 135 1575 Cell[redacted] Fax: +27(0) 86 270 8737 E-mail: wbrumskine@auruminstitute.org Contact Person: Dr William Lawrence Brumskine **Site 13** Site name: Emavundleni Research Centre, Dr Gonasgrie Nair Physical Address: 14 Sonwabile Drive, Old Crossroads, Klipfontein, 7750, Cape Town, South Africa Emavundleni Additional Location Research Centre. Hob 38 (Ground Floor), Philippi Crescent, Philippi, 7781, Cape Town, South Africa Contact Details: Tel: +27(0) 21 650 5851 Cell[redacted] Fax: +27(0) N/A E-mail: lulu.nair@hiv-reserach.org.za Contact Person: Dr Gonasgrie Nair

	Site 14 Site name: Synexus SA - Stanza Clinical Research Centre, Dr Sheena Kotze (née Steyl) Physical Address: 02 Shilovhane street, Mamelodi East, Pretoria, Gauteng, 0122, South Africa Contact Details: Tel: +27(0) 12n942 7357 Cell[redacted] Fax: +27(0) 86 724 7516 E-mail: sheena.kotze@synexus.com Contact Person: Dr Sheena Kotze **Site 15** Site name: Themba Lethu HIV Research Unit (CHRU), Dr Sharlaa Badal-Faesen Physical Address: University of Witwatersrand, Clinical HIV Research Unit (CHRU), Themba Lethu Clinic, Helen Joseph Hospital, Perth Road, Westdene, Johannesburg South Africa Contact Details: Tel: +27(0) 11 276 8800 Cell[redacted] Fax: +27(0) 11 482 2130 E-mail: sfaesen@witshealth.co.za Contact Person: Dr Sharlaa Badal-Faesen **Site 16** Site name: CAPRISA eThekwini Clinical Research Site, Dr Nivashnee Naicker Physical Address: No. 3 Richards Road, Warwick Avenue, Berea, Durban, 4001, KwaZulu-Natal, South Africa Contact Details: Tel: +27(0) 31 655 0618 Cell[redacted] Fax: +27(0) N/A E-mail: Nivashnee.naicker@caprisa.org Contact Person: Dr Nivashnee Naicker **Site 17** Site name: Desmond Tutu Health Foundation - Masiphumelele Research Office, Dr Katherine Margaret Gill Physical Address: Guinea Fowl Road, Sunnydale, 7975 Contact Details: Tel: +27(0) 21 785 3121 Cell[redacted] Fax: +27(0) 21 785 3121 E-mail: katherine.gill@hiv-research.org.za Contact Person: Dr Katherine Margaret Gill

	Site 18 Site name: Perinatal HIV Research Unit (PHRU), Dr Fatima Laher Physical Address: New Nurses Home, Chris Hani Baragwanath Academic Hospital, Chris Hani Road, Soweto, 1862, South Africa Contact Details: Tel: +27(0) 11 989 9720 Cell [redacted] Fax: +27(0) 11 989 9762 E-mail: laherf@phru.co.za Contact Person: Dr Fatima Laher **Site 19** Site name: Khayelitsha CRS, Dr Amy Ward Physical Address: Site B CHC, 98 Sulani Drive, Khayelitsha, 7784, South Africa Contact Details: Tel: +27(0) 21 650 5530 Cell [redacted] Fax: +27(0) 21 4066 796 E-mail: amyward41@gmail.com Contact Person: Dr Amy Ward **Site 20** Site name: Tongaat Clinical Research Site, Dr Vimla Naicker Physical Address: South African Medical Research Council, HIV Prevention Research Unit, 12-14 Tesco Drive, Tongaat, KwaZulu Natal, South Africa, 4400 Contact Details: Tel: +27(0) 32 944 2208 Cell [redacted] Fax: +27(0) 32 944 3379 E-mail: vimla.naicker@mrc.ac.za Contact Person: Dr Vimla Naicker **Site 21** Site name: South African Vaccine Initiative (SATVI), Dr Angelique Kany Kany Luabeya Physical Address: Project Office, Brewelskloof Hospital Haarlem Street Worcester, 6850, South Africa Contact Details: Tel: +27(0) 23 346 5400 Cell [redacted] Fax: +27(0) 23 346 5406 E-mail: Angelique.luabeya@uct.ac.za Contact Person: Dr Angelique Kany Kany Luabeya

	Site 22 Site name: CAPRISA Vulindlela Clinical Research Site, Dr Disebo Makhaza Physical Address: adjacent to Mafakatini Primary Healthcare Clinic, Road P402, Ward 9, uMgungundlovu District, KwaZulu Natal, South Africa Contact Details: Tel: +27(0) 31 655 0687 Cell[redacted] Fax: +27(0) N/A E-mail: disebo.makhaza@caprisa.org Contact Person: Dr Disebo Makhaza **Site 23** Site name: CRISMO Research Centre, Dr Musawenkosi Bhekithemba Mamba Physical Address: Bertha Gxowa Hospital, Villa Heidi Building, Joubert and Hospital Street, Germiston, 1401, Gauteng, South Africa Contact Details: Tel: +27(0) 11 038 6814 Cel[redacted] Fax: +27(0) 86 515 2345 E-mail: drmamba@crismo.co.za Contact Person: Dr Musawenkosi Bhekithemba Mamba **Site 24** Site name: Botha's Hill Clinical Research Site, Dr Elizabeth Spooner Physical Address: South African Medical Research Council, HIV Prevention Research Unit, No. 1 Zulu Road, Valley Trust, Botha's Hill, Kwa-Zulu Natal, 3660 Contact Details: Tel: +27(0) 31 777 1585 Cell[redacted] Fax: +27(0) 31 7771084 E-mail: Elizabeth.Spooner@mrc.ac.za Contact Person: Dr Elizabeth Spooner

	Site 25 Site name: Synexus Watermeyer Clinical Research Centre, Dr Elane van Nieuwenhuizen Physical Address: 60 Stamvrug Street, Val de Grace, Pretoria, Gauteng, 0184 Contact Details: Tel: +27(0) 12 803 7733 Cell [redacted] Fax: +27(0) 86 724 7498 E-mail: elane.vannieuwenhuizen@synexus.com Contact Person: Dr Elane van Nieuwenhuizen **Site 26** Site name: Synexus Helderberg Clinical Research Centre, Dr Dorothea Vera Urbach Physical Address: Suite 7G & H Arun Place, Sir Lowry's Pass Road, Somerset West,7130, South Africa Contact Details: Tel: +27(0) 21 850 1039 Cel [redacted] Fax: +27(0) 21 850 1034 E-mail: dorothea.urbach@synexus.com Contact Person: Dr Dorothea Vera Urbach **Site 27** Site name: Nelson Mandela Academic Clinical Research Unit (NeMACRU), Dr Thozama Dubula Physical Address: Sir Henry Elliot Hospital, 17 Hospital Road, Mthatha, Eastern Cape, South Africa, 5099 Contact Details: Tel [redacted] Cel [redacted] Fax: 087 809 6032 E-mail: tdubula@witshealth.co.za Contact Person: Dr Thozama Dubula **Site 28** Site name: MeCRU Clinical Research Unit, Prof Maposhane Nchabeleng Physical Address: Sefako Makgatho Health Science University, Medunsa, Gauteng, South Africa, 0204 Contact Details: Tel: 012 521 5667 Cell [redacted] Fax: 012 521 3035 E-mail: maphoshane.nchabeleng@smu.ac.za Contact Person: Prof Maposhane Nchabeleng

	Site 29 Site name: Mzansi Ethical Research Centre: Middleburg, Dr Friedrich Petrick Physical Address: 184 Cowen Ntuli Street, Middleburg, Mpumalanga, South Africa, 1055 Contact Details: Tel: 013 282 5218 Cell [redacted] Fax: 013 243 0328 E-mail: fgpetrick@merc.za.net Contact Person: Dr Friedrich Petrick **Site 30** Site name: Ndlovu Research Centre, Dr Rebone Maboa Physical Address: Plot 1140 Elandsdoorn, Dennilton, Limpopo, South Africa, 0470 Contact Details: Tel: 013 983 8700 Cell [redacted] Fax: 013 983 8757 E-mail: rmaboa@ndlovu.com Contact Person: Dr Rebone Maboa **Site 31** Site name: Wits RHI: Shandukani Research Centre, Dr Faeezah Patel Physical Address: 2nd Floor: Hillbrow Health Precinct, Corner Esselen Street and Klein Street, Hillbrow, Johannesburg, Gauteng, South Africa, 2001 Contact Details: Tel: 011 358 5300 Cell [redacted] Fax: 086 548 4889 E-mail: FPatel@wrhi.ac.za Contact Person: Dr Faeezah Patel
2.2 Details of how sites were selected	In order to support the national SARS-COV-2 vaccine prevention program, Department of Health Vaccine administration sites across South Africa supported by the Ensemble Research Site Investigators and study staff were selected. All principal investigators chosen are experienced investigators who participated in the ENSEMBLE VAC31518COV3001 Protocol - *A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older*. Their sites are well structured for performing clinical trial related operations and have experienced staff to conduct the study. The sites were initially selected based on their capacity, resources and access to required participant populations for the VAC31518COV3001 Protocol and can continue providing support in this study. Many of the sites also participated in the HIV vaccine trials using the same Ad26 vector.

<table>
<tr><td>2.3 Details of investigators and staff (Investigators, staff, number of staff, names, qualifications, experience)</td><td>Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application</td></tr>
<tr><td>2.4 Details of capacity of site(s):
(site facilities, equipment, emergency facilities, other relevant infrastructure and investigator work load documents)</td><td>Refer to ENSEMBLE VAC31518COV3001 Protocol CTF1 Application</td></tr>
<tr><td>2.5 Details and evidence of competence of the laboratories:
• Collection and processing of samples for shipping to centralised testing facilities (include conditions of shipping)
• Bedside/point-of-contact testing and details of training of staff
• Screening and safety testing of clinical samples during the trial
• Specialised end-point testing (virology, immunology, cytokine analysis)</td><td>Collection and processing of samples:
Samples will be obtained from participants, prepared and transported from sites to the National Health Laboratory Services (NHLS).

The samples will either be transported ambient, refrigerated or frozen as applicable for the specific sample as required.

Sampling will be performed by suitably qualified site staff delegated by the principal investigator.

The following Protocol-Required Laboratory Assessments will be performed in accordance with the schedule of activities in the sub-cohort:
<table><tr><th>Laboratory Assessments</th><th>Parameters</th><th>Time points</th></tr><tr><td>Testing done</td><td>(1) Nasal swabs for virology testing (molecular confirmation Of SARS-CoV-2)</td><td>At baseline and follow up</td></tr><tr><td></td><td>(2) Serology blood sample for sero-confirmation of SARS-CoV-2 infection in a sub-set of participants (approx 10 000)</td><td>On day of vaccination and follow up</td></tr><tr><td></td><td>(3) RNAseq blood sample for exploration of biomarkers correlating with SARS-CoV-2 infection and COVID-19 severity in participants with breakthrough infection (PAXgene tubes, whole blood)</td><td>As soon as possible after identification of the breakthrough infection</td></tr><tr><td></td><td>(4) Nasal swab virology testing (other respiratory pathogens) using a broad respiratory pathogens panel</td><td>May be performed on samples collected during a confirmed COVID-19 episode and in a subset of samples from participants with asymptomatic infection.</td></tr><tr><td></td><td>(5) Blood samples for neutralization assays and immune responses</td><td>At baseline and follow up visits</td></tr></table></td></tr>
</table>

<table>
<tr><th colspan="2">PART 3: REGULATORY DETAILS</th></tr>
<tr><td>3.1 Name other Regulatory Authorities/Ethics Committees to which application to do this trial have been submitted, and/or approved</td><td>This application will be sent to the local ethics committees including: University of the Witwatersrand Human Research Ethics Committee (Wits HREC), Pharma-Ethics, University of Cape Town Human Research Ethics Committee (UCT HREC), South African Medical Research Council (SAMRC) Human Research Ethics Committee, University of KwaZulu-Natal Biomedical Research Ethics Committee, University of Stellenbosch Ethics Committee, Sefako Makgatho University Research Ethics Committee (SMUREC).</td></tr>
</table>

3.2 If the trial is to be conducted in SA and not in the host country of the applicant / sponsor, provide an explanation	The previous VAC31518COV3001 ENSEMBLE Protocol was conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and the United States. This ENSEMBLE Open Label implementation study is designed specifically to monitor the effectiveness of the single shot Ad26.COV2.S COVID-19 vaccine among health care workers in South Africa. South Africa is severely affected by the global COVID-19 epidemic, but currently no vaccine has been rolled out. The recent results of the 'ENSEMBLE' trial conducted by Janssen in South Africa and abroad, and the availability of a limited amount of vaccine doses, provide the rationale for a cohort study of vaccinated Health Care Workers to inform the larger vaccine rollout.
3.3 Name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection	Not Applicable
3.4 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities	Not Applicable

SECTION 2: CLINICAL TRIAL PROTOCOL

PART 4: INVESTIGATIONAL PRODUCT (IP) AND OTHER MEDICINES	
4.1 Details of IP (name, strength, formulation, dose(s), mode of administration and other relevant IP details)	Name: Ad26.COV2.S Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) spike (S) protein. Ad26.COV2.S is produced in PER.C6-TetR cells. Ad26.COV2.S will be supplied at a concentration of 1×10^{11} vp/mL in single-use vials, with an extractable volume of 0.25 mL, and dosed at 5×10^{10} vp. Study vaccine will be administered by IM injection into the deltoid muscle, preferably of the non-dominant arm. If an injection cannot be given in the deltoids due to a medical or other contraindication use alternative locations such as the hip, thigh or buttocks (to be avoided in overweight participants). Study vaccine administration must be captured in the electronic system Ad26.COV2.S will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. Vaccine Compliance: Study vaccines will be administered intramuscularly by a study vaccine administrator – a trained and qualified study nurse, medical doctor, or otherwise qualified healthcare professional. The pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing. The date of each study vaccine administration will be recorded in the appropriate CRF. Treatment of Overdose For this study, any dose of Ad26.COV2.S greater than the assigned dose will be considered an overdose. The vaccine manufacturer does not recommend specific treatment for an overdose. In the event of a known overdose, the investigator should: • Contact the safety physician immediately. • Closely monitor the participant for AE/SAE/MAAE (ie, the participant will remain at the study site for at least 1 hour and will be closely monitored for allergic or other reactions by study staff. Follow-up telephone calls 12 hours and 24 hours post-dose may be made.

	• Document the quantity of the excess dose in the source document. • Report as a special reporting situation. Ad26.COV2.S is not registered in South Africa
4.2 Properties of IP i.e. mechanism of action	Ad26.COV2.S (VAC31518, JNJ-78436735) is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the SARS-CoV-2 Spike (S) protein. The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate vaccines against SARS-CoV, and the common conclusion that has emerged is that the viral S protein is the only significant target for neutralizing antibodies and the only viral protein that can elicit protective immunity in animal models. In a clinical study with a deoxyribonucleic acid (DNA) vaccine encoding SARS-CoV S protein, neutralizing antibody responses were detected in all study participants who received 3 doses of vaccine. All currently identified anti-SARS-CoV neutralizing monoclonal antibodies target the viral S protein; most target the receptor binding domain, while a few target other regions in the S protein. The S protein was also a target for neutralizing antibodies in convalescent sera of individuals recovered from SARS or MERS. Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen. This choice has been supported by recent publications that describe neutralizing antibodies targeting the SARS-CoV-2 S protein. Ad26.COV2.S encodes a membrane-bound full-length S protein derived from a SARS-CoV-2 clinical isolate (Wuhan, 2019, whole genome sequence NC_045512), with 2 amino acid changes in the S1/S2 junction that knock out the furin cleavage site, and 2 proline substitutions in the hinge region. These mutations are based on earlier designs of soluble S proteins from MERS-CoV and SARS-CoV, and are known to stabilize the prefusion conformation of soluble SARS-CoV-2 S protein. These modifications were shown to increase the induction of neutralizing antibodies compared with wild-type (wt) S protein in nonclinical studies.
4.3 Summary of Pre-clinical findings (e.g. laboratory / animal / toxicity / mutagenicity)	Nonclinical Pharmacology Nonclinical immunogenicity studies were performed in mice, rabbits, Syrian hamsters, and nonhuman primates. Efficacy studies were performed in Syrian hamsters and nonhuman primates (NHP). A single dose of Ad26.COV2.S induced SARS-CoV-2 binding and neutralizing antibodies in all test species. In response to vaccination with Ad26.COV2.S, the Th1-associated cytokine interferon gamma (IFN-γ) was produced in mice, rabbits, and NHP. In mice, a single dose of Ad26.COV2.S induced a Th1-skewed immune response, characterized by the induction of IgG2a antibodies and the ratio of Th1 to Th2 associated cytokines. In the Syrian hamster SARS-CoV-2 challenge model, a single dose of Ad26.COV2.S resulted in lower viral load in the lung and reduced body weight loss after SARS-CoV-2 challenge. In the NHP SARS-CoV-2 challenge model, viral load in the

	lower respiratory tract was below the limit of detection in all NHP immunized with Ad26.COV2.S (N=6). Viral load in the upper respiratory tract was below the limit of detection in 5 out of 6 NHP. More details of the nonclinical immunogenicity and efficacy studies are provided in the investigators brochure and investigators brochure addendum included with this submission. Nonclinical Safety Biodistribution To assess distribution, persistence, and clearance of the Ad26 viral vector platform, intramuscular (IM) biodistribution studies have been conducted in rabbits using an Ad26-based HIV vaccine, Ad26.ENVA.01, and an Ad26-based RSV vaccine, Ad26.RSV.preF. In the available biodistribution studies, the Ad26 vector did not widely distribute following IM administration in rabbits. Ad26 vector deoxyribonucleic acid (DNA) was primarily detected at the site of injection, draining lymph nodes and (to a lesser extent) the spleen. Clearance of the Ad26 vector from the tissues was observed. Both Ad26 vectors showed a comparable biodistribution profile despite carrying different antigen transgenes. These data further indicate that the Ad26 vector does not replicate and/or persist in the tissues following IM injection. These platform data are considered sufficient to inform on the biodistribution profile of Ad26.COV2.S for which the same Ad26 vector backbone is used. Toxicology The sponsor has significant nonclinical experience with Ad26-vectored vaccines using various transgenes encoding HIV, RSV, Ebola virus, filovirus, human papilloma virus, Zika, influenza (universal flu [Uniflu]), and malaria antigens. To date, more than 10 Good Laboratory Practice (GLP) combined repeated dose toxicology and local tolerance studies have been performed in rabbits (and 1 study in rats), testing the nonclinical safety of various homologous and heterologous regimens with Ad26-based vaccines at full human doses up to 1.2×1011 vp. No adverse effects have been observed in these studies. The vaccine-related effects observed were similar across studies, considered to be reflective of a physiological response to the vaccines administered, and seem to be independent of the antigen transgene. Overall, there were no safety signals detected in any of the available GLP toxicology studies with Ad26-based vaccines up to the highest dose tested (1.2×1011 vp). In a combined embryo-fetal and pre- and postnatal development GLP study in female rabbits with another Ad26-based vaccine (Ad26.ZEBOV, encoding an Ebola virus antigen), there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period. A repeated dose and local tolerance GLP study, and a combined embryo-fetal and pre- and postnatal development GLP study with Ad26.COV2.S are planned to run in parallel with study VAC31518COV1001

4.4 Summary of Clinical Findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other).	FIH VAC31518COV1001(Phase1-2a) As of September 2020, a single injection of Ad26.COV2.S had been administered to 805 adult participants, aged 18 and older in a phase 1-2a study at centers in Belgium and USA. The FIH VAC31518COV1001 study is a phase 1-2a trial of healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3) to receive the Ad26.COV2.S vaccine at a dose of 5×1010 viral particles (low dose) or 1×1011 viral particles (high dose) per ml or placebo in a single-dose or two-dose schedule. Cohort 2 collected longer-term data comparing the single -dose regimen with the two-dose regimen. The primary end points were the safety and reactogenicity of each dose schedule. In the preliminary report of cohort 1 and 3, for the 805 participants receiving the first dose, frequent solicited adverse events were headache, fatigue, myalgia and injection site pain. Fever occurred more commonly amongst the systemic symptoms. Systemic adverse events were lesser in cohort 3 vs. cohort 1 and a similar picture was observed in those receiving a lower dose compared to higher dose. Reactogenicity was lower following the second dose. In at least 90% of participants, neutralization against the wild type virus was demonstrated on day 29 pot-vaccination dose (geometric mean titer [GMT], 224 to 354). This was regardless of age group or dose of vaccine. These titres increase by day and reached 100% by day 57 with additional increase in titres in cohort 1a (GMT, 288 to 488). Titres remained stable until at least day 71. Administration of the second dose, resulted in 2.6 to 2.9 fold increases of titre (GMT 827 TO 1266). There was no difference between spike-binding antibody responses and neutralizing antibody responses. CD4+ T-cell responses were detected in 76-83% of cohort 1 participants and in 60-70% of those in cohort 3 in day 14. There was skewing toward the type 1 helper T cells. Overall, CD8+ T-cell responses were robust with some attenuation in cohort 3. The single dose of Ad26.COV2.S elicited strong humoral response in most of the vaccine recipients, including the presence of S-binding and neutralizing antibodies in at least 90% of the participants regardless of age or dose. The increasing and stabilizing antibody titres further point to a durable immune response. These findings, including that of an acceptable safety profile, supported the decision to proceed with two phase 3 trials (Ensemble and Ensemble 2) to evaluate the efficacy of either a single-dose or two-dose regimen of the lower dose (5×1010 viral particles) of Ad26.COV2.S.

	VAC31518COV3001 – Ensemble (Phase 3) As of January 2021, approximately 44,000 adult participants had received a single-dose of Ad26.COV2.S in the Ensemble Phase 3 trial conducted across four continents (approximately 6,600 in South Africa). Ensemble is a Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older. Participants were randomized in parallel in a 1:1 ratio to receive intramuscular (IM) injections of Ad26.COV2.S or placebo. Ad26.COV2.S was administered at a dose level of 5×10^{10} vp. The trial is fully enrolled. The primary objective is to demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed, moderate to severe/critical coronavirus disease-2019, as compared to placebo, in SARS-CoV-2 seronegative adults. For the primary objective, all moderate to severe/critical COVID-19 cases are considered. As a secondary objective, VE in the prevention of asymptomatic SARS-CoV-2 infection and mild COVID-19 is analyzed. An immunologic test for SARS-CoV-2 seroconversion (ELISA and/or SARSCoV-2 immunoglobulin assay) based on SARS-CoV-2 N protein, is being performed to identify cases of asymptomatic infection. This assay is performed on samples obtained at Day 1 (pre-vaccination), Day 71, 6 months, and 1 year after vaccination. A total of approximately 400 participants form the Immunogenicity Subset (ie, 400 participants at sites with access to appropriate processing facilities), blood is collected for analysis of humoral immune responses at Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year, 18 months, and 2 years after vaccination. The first 2,000 participants in each of the 2 age groups form the part of the safety subset and remained under observation at the study site for at least 30 minutes post-vaccination to monitor for the development of acute reactions. The trial is ongoing and at the time of writing, preliminary results showed the single-dose vaccine candidate had an acceptable safety profile and was found to demonstrate 66% effectiveness overall against in preventing moderate and severe COVID -19 disease, as of 28 days after vaccination globally (72% in the USA and 57% in South Africa). It was 85% effective overall in preventing severe disease, and there were no COVID-19 related hospitalizations and deaths, including in South Africa. Importantly, there was a high level of protection observed against severe disease cause by the SARS-CoV-2 variant from the B.1.351 variant lineage observed in South Africa (89% as of 28 days). This single - dose vaccine candidate is estimated to remain stable for two years at -20°C, at least three months of which can be at temperatures of 2-8°C.

	VAC31518COV3009 ENSEMBLE 2 (Phase 3) This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 years of age. The efficacy, safety, and immunogenicity of Ad26.CoV2.S is being evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of 2 doses of study vaccine. Even though a single-dose regimen in study VAC31518COV1001 showed good immunogenicity that may already protect against COVID-19, data from other vaccines using the Ad26 platform suggest that a second vaccination may potentially result in an increased and more durable immune response, providing justification for the evaluation of a 2-dose regimen in this study. Participants will be randomized in parallel in a 1:1 ratio to receive intramuscular (IM) injections of Ad26.COV2.S or placebo. Ad26.COV2.S will be administered at a dose level of 5×10^{10} vp. Endpoints are largely similar to the 1 dose ENSEMBLE trial. At the time of this submission, the trial is currently ongoing.
4.5 Details of comparator medicine(s) (name strength, formulation, dose(s), mode of administration and justification of the choice of the comparator)	Not Applicable
4.6 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required or excluded in the protocol	Not Applicable
4.7 Registration status of IP, concomitant and/or comparator medicine(s) (include Investigator's brochure, SAHPRA approved PI, and other international professional information (package inserts) if not approved in SA and certificate of analysis)	The study medication Ad26.COV2.S is not registered in South Africa by the SAHPRA.
4.8 Estimated Quantity of Trial Material (each medicine detailed separately) for which exemption will be required (including overage and justification for overage if above 20%)	We anticipate vaccinating up to 500 000 health care workers/participants in this open label phase 3B vaccine trial. 1 vial of Ad26.COV2.S **(**concentration of 1×10^{11} vp) = 2 doses of 5×10^{10} vp at 0.25ml/dose

	Therefore a minimum of 250 000 vials Ad26.COV2.S will be required. We have factored in a 20% overage to account for unanticipated events and as this is part of the national rollout strategy the following quantities are requested. **ESTIMATED QUANTIY OF STUDY PRODUCT REQUIRED AND TO BE NOTED ON SAHPRA APPROVAL LETTER :** **500 000 VIALS Ad26.COV2.S (concentration of 1×10^{11} vp)**
4.9 If any of the above medicines are available in South Africa, give an explanation why they need to be imported from elsewhere	Not applicable, the investigational product is not registered or commercially available in South Africa.
4.10 Details of medicine(s) supply management and accountability (receipt of medicine(s) from supplier, storage, dispensing, packaging and labelling of Investigational Product)	The study medicine will be stored, distributed, labelled and dispensed according to the applicable legislation within the Medicines Act 101 of 1965 as amended and the Pharmacy Act 88 of 1974 as amended. All persons dispensing the medication will be licensed to dispense in terms of the Medicines Act 101 of 1965 as amended. Supply management Drug Product Manufacturers: Janssen Vaccines AG (Branch of Cilag GmbH International) Bern, Switzerland Vibalogics GmbH, Cuxhaven, Germany IDT Biologika GmbH Dessau-Rosslau Germany The study vaccines will be packaged according to good manufacturing practices and local regulations. The study vaccines will not be packed in individual participant kits, one kit will be used by multiple participants. Each kit will contain single- use vials. Study vaccine labels will contain information to meet the applicable regulatory requirements. All study vaccines will be labeled under the responsibility of the manufacturer. No study vaccine can be relabeled without prior approval of the manufacturer Preparation/Handling/Storage All study vaccine must be stored in a secured location with no access for unauthorized personnel and at controlled temperatures as indicated on the clinical labels. If study vaccine is known to be exposed to temperatures outside the specified temperature range, all relevant data will be sent to the manufacturer to determine if the affected supplies can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

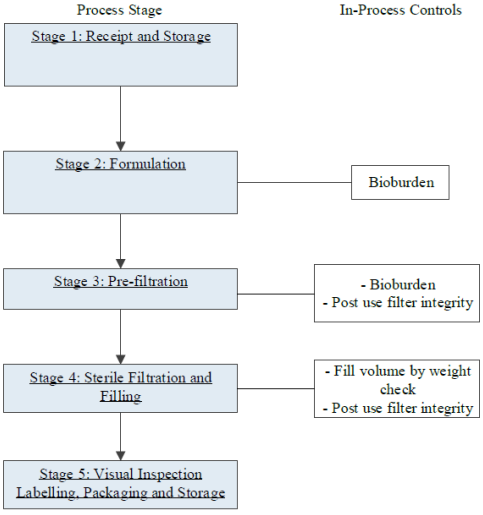
	Refer to the study site investigational product and procedures manual (SIPPM) and the Investigational Product Preparation Instructions (IPPI) for additional guidance on study vaccine preparation, handling, and storage. A study-site pharmacist, or other qualified individual, who will have no other study function following vaccination, will prepare the appropriate syringes for vaccine administration. Accountability The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the vaccination card with the batch number. All study vaccine will be stored and disposed of according to manufacturer instructions. Needles and syringes will be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes. Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist or national rollout vaccine nurse. Study vaccine will be administered only to participants participating in the study.
4.11 Give details of intention to register and justify if registration is not envisaged	Not Applicable – SAMRC do not hold the license to register the vaccine.
4.12 Details of the manufacture, quality control and stability of the IP	Ad26.COV2.S Investigational Product Product general information Ad26.COV2.S (VAC31518, JNJ-78436735; until recently also named Ad26COVS1) is a monovalent, recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike (S) protein. The composition of the Ad26.COV2.S drug product is provided in below. Composition of Ad26.COV2.S drug product **Ingredient** / **Function** Ad26.COV2.S – Active ingredient Sodium chloride – Tonicity agent and stabilizer Citric acid monohydrate – Buffer Polysorbate 80 – Stabilizer 2-hydroxypropyl-b-cyclodextrin (HBCD) – Stabilizer Ethanol (absolute) – Stabilizer Sodium hydroxide – pH adjuster Water for Injection (WFI) – Diluent The pharmaceutical presentation is a suspension for injection to be administered via intramuscular (IM) injection. It is supplied as a single-dose suspension filled in Type I glass vials from which an 0.50 mL extractable volume is ensured. Vials are closed with chlorobutyl rubber stoppers and aluminum flip-off caps. The drug product (DP) titer is 2.0×10^{11} Virus Particles (VP)/mL and the vaccine product at

the manufacturing site is stored frozen at -85°C to -55°C. Once the vaccine is transported it can be stored frozen at -20°C. At the clinical site, DP storage is allowed at +2° to +8°C for a maximum period of 1 month.

Manufacture

A flow diagram of the manufacturing process of the DP together with the IPC performed during the DP manufacturing process is provided in below. An IPC is defined as tests, checks and measurements made during manufacturing to monitor and, if necessary, adjust the process to ensure the resulting DP will comply with its specification. Manufacturing is performed according to cGMP and the facilities are in possession of the relevant licenses.

Flow Diagram of Ad26.COV2.S Drug Product Manufacturing and In-Process Controls



Quality Control

Specifications for release testing of Ad26.COV2.S DP are listed in below.

Specifications for Release Testing of Ad26.COV2.S Drug Product

Attribute	Test Method	Release
Appearance and description		
Appearance: degree of coloration	Ph. Eur. *2.2.2*	<Reference solution B7, BY5, Y5, and
Appearance: clarity	Ph. Eur. *2.2.1*	<Reference suspension IV
Appearance: visible particles	Ph. Eur. *2.9.20*	Essentially free of visible particulate m
Identity		
Virus identity	ID-PCR	Identity confirmed
Virus protein fingerprinting	RP-HPLC	Identity confirmed
Potency		
Transgene expression	ELISA (Qualitative)	Expression confirmed
Infectious units	QPA	≥8.60 $\log_{10}$ IU/mL
Quantity		
Virus particles (vector concentration)	VP-qPCR	
Target 1.0×10^{11} VP/mL Target 2.0×10^{11} VP/mL[a]		$0.6–1.6 \times 10^{11}$ VP/mL $1.3–3.2 \times 10^{11}$ VP/mL[a]
Safety		
Sterility	Ph. Eur. *2.6.1*, USP<71> (Membrane filtration)	No Growth
Bacterial endotoxin	Ph. Eur. *2.6.14*	≤10 EU/mL
Container closure integrity	Ph. Eur. *3.2.9*, USP<1207> (Dye ingression)	NA
General		
pH	Ph. Eur. *2.2.3*, USP <791>	6.0–6.4
Osmolality	Ph. Eur. *2.2.35*, USP <785>	280–380 mOsmol/kg
Extractable volume	Ph. Eur. *2.9.17*	?0.50 mL

(a) This is the strength that will be used in the COV3001 clinical trial

NA= Not applicable; ELISA= Enzyme-linked Immunosorbent Assay; ID-PCR= Identity polymerase chain reaction; QPA= Quantitative potency assay; VP-qPCR= Virus particle quantitative polymerase chain react RP-HPLC= Reversed Phase High-pressure Liquid Chromatography

	Stability The stability profile of the Ad26.COV2.S is currently being monitored at different storage conditions (-60°C; -20°C; +5°C; +25°C). Based on other Ad26 vaccine drug products (platform knowledge), the following shelf-lives are supported: • 24 months when stored at -85°C to -55°C • 12 months when stored at -20°C • 3 months when stored at +2°C to +8°C
4.13 Previous studies using this medicine which have been approved by SAHPRA* and include SAHPRA* approval number Study title, Protocol number, Date of approval, National PI / Principal Investigator, Date(s) Progress report(s) and Date Final report)	Study Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older SAHPRA trial reference: 20200434 Protocol number: VAC31518COV3001 Date of Approval: 22 September 2020 National PI: Profs Glenda Gray and Linda-Gail Bekker Date of last progress report: December 2020 The following studies using the Ad26 vector have been approved by SAHPRA Other studies using the Ad26 vector: Study title: A Phase 1/2a Study to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Vaccine Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Vaccine Regimens, with High-Dose, Low-Dose or no Clade C gp140 Protein Plus Adjuvant for HIV Prevention SAHPRA trial reference: 20150105 Protocol number: HIV-V-A004 Date of Approval: 18 May 15 National PI: Dr F Laher Date of last progress report: 17 Mar 20 Last DAFF progress report: 04 Jun 20 Last IBC progress report : 04 Jun 20 Study title: A multicenter, randomized, double-blind, placebo-controlled phase 2b efficacy study of a heterologous prime/boost vaccine regimen of Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 in preventing HIV-1 infection in women in sub-Saharan Africa SAHPRA trial reference: 20170520 Protocol number: VAC89220HPX2008 Date of Approval: 29 Aug 17 National PI: Prof Glenda Gray Date of last progress report: 22 Apr 20

**This include all studies approved in the previous SAHPRA dispensation called Medicines Control Council*

PART 5: BACKGROUND INFORMATION	
5.1 Disease / problem in South African context (e.g. local epidemiology)	SARS-CoV-2 is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus. It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019. Early epidemiological investigations suggested that the majority of early cases were linked to a seafood market, with patients infected through zoonotic or environmental exposure, followed by the subsequent spread of infection by human-to-human transmission among close contacts. However, there is some controversy about the initial origin of the virus. Genomic sequencing was performed on bronchoalveolar lavage fluid samples collected from patients with viral pneumonia admitted to hospitals in Wuhan, which identified a novel RNA virus from the family Coronaviridae. Phylogenetic analysis of the complete viral genome revealed that the virus, SARS-CoV-2, is part of the subgenus Sarbecovirus of the genus Betacoronavirus, and is most closely related (approximately 88% identity) to a group of SARS-CoV-like coronaviruses previously sampled from bats in China. SARS-CoV-2 has spread rapidly and globally since its emergence. The World Health Organization (WHO) declared that the outbreak constituted a public health emergency of international concern on January 30, 2020, and declared the outbreak to be a pandemic on March 11, 2020. As of June 1, 2020, approximately 6,680,000 cases of COVID-19 and approximately 375,000 COVID-19-related deaths have been reported. Symptoms of infection may appear from 2 to 14 days following exposure, with the clinical manifestations ranging from mild symptoms to severe illness or death. Severe clinical presentations have been reported in as many as 20 to 25% of laboratory-confirmed cases.24 In a study of 99 patients in a single center in Wuhan with SARS-CoV-2 infection confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR), the most commonly reported clinical manifestations were fever (83%), cough (82%), shortness of breath (31%), and muscle aches (11%). In chest X-rays and computed tomographic (CT) scans, 75% of patients showed bilateral pneumonia and 14% of patients showed diffuse mottling and ground-glass opacities. In a further study of 138 patients with novel coronavirus-induced pneumonia in a single center in Wuhan, common symptoms included fever (98.6%), fatigue (69.6%), and dry cough (59.4%). Lymphopenia occurred in 70.3% of patients, and chest CT scans showed bilateral patchy shadows or ground-glass opacities in the lungs of all patients. Thirty-six patients (26%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome, arrhythmia, and shock. Subsequent United States

	(US) Centers for Disease Control and Prevention (CDC) descriptions of COVID-19 clinical case definitions and Janssen-sponsored interviews with COVID-19-experienced clinicians have included signs and symptoms of respiratory distress such as blue lips, extreme shortness of breath and dyspnea, persistent cough, deep vein thrombosis, Kawasaki-like disease, discoloration of feet and toes, chills, shaking chills, loss of sense of taste and smell, signs of stroke, disorientation, inability to respond or understand verbal communication, among others. At present, it appears that individuals aged ≥65 years, especially those with comorbid diseases, are subject to the highest incidence of morbidity and mortality. In contrast, a study of 2,143 children aged <18 years in China with laboratory-confirmed (34.1%) or suspected (65.9%) COVID-19 indicated that the clinical manifestations of the disease may be less severe in children than adults, with approximately 94% of cases being asymptomatic, mild, or moderate. However, young children, particularly infants, were susceptible to severe disease, with the highest proportion of severe and critical cases by age group reported for children aged <1 year (10.6% of cases in this age group). A study of 149,082 COVID-19 cases reported in the US was consistent with these findings. Only 1.7% of these cases occurred in persons aged <18 years although this age group accounts for 22% of the US population. Furthermore, relatively few pediatric COVID-19 cases were hospitalized, indicating that COVID-19 might have a mild course among younger patients. Hospitalization was most common among pediatric patients aged <1 year and those with underlying conditions. Recent (April-May 2020) reports describe several cases of multisystem inflammatory syndrome (MIS) in children with Kawasaki disease-like features (ie, fever, laboratory markers of inflammation, severe illness requiring hospitalization, multisystem organ involvement). Most of these children had tested positive for current or recent SARS-CoV-2 infection or were linked to a COVID-19 case. It is currently unknown if MIS is specific to children or if it may also occur in adults. The identification of SARS-CoV-2 follows the emergence of 2 other novel betacoronaviruses capable of causing severe human disease over the past 18 years: SARS-CoV and MERS-CoV, which have nucleotide sequence identity with SARS-CoV-2 of approximately 79% and 50%, respectively. The first known cases of severe acute respiratory syndrome (SARS) occurred in Southern China in November 2002. The etiological agent, SARS-CoV, is believed to be an animal virus that crossed the species barrier to humans followed by human-to-human transmission, leading to SARS cases in >25 countries. The MERS-CoV was isolated from a patient in Saudi Arabia who died of severe pneumonia and multi-organ

	failure in June 2012. MERS-CoV is considered to be a zoonotic virus capable of non-sustained human-to-human transmission. Since 2012, sporadic cases and community and health-care-associated clusters of infected individuals have been reported in the Middle East. Patients with SARS or Middle East respiratory syndrome (MERS) present with various clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory disease with extrapulmonary manifestations. Both diseases have predominantly respiratory manifestations, but extrapulmonary features may occur in severe cases. By July 2003, the international spread of SARS-CoV resulted in 8,098 SARS cases and 774 deaths (case-fatality rate: 10%) with substantial social, economic and health service disruption in some affected countries. The case-fatality rate of MERS-CoV infections is estimated to be 35%. It is not known if SARS-CoV-2 will remain as a worldwide pandemic. It is also not known if immunity is acquired after symptomatic or asymptomatic SARS-CoV-2 infection and howlong it might last. Currently, the only preventive measures that have been employed with some success have been social distancing and quarantine after contact tracing and testing. Test and treat approaches await an effective proven safe therapy that can be implemented on a mass scale. It is generally believed that an effective vaccine will be 1 of the most important tools to help control this highly contagious respiratory virus. South Africa: The COVID-19 pandemic in South Africa is part of the ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 5 March 2020, Minister of Health Zweli Mkhize confirmed that the virus spread to South Africa, with the first known patient being a male citizen who tested positive upon his return from Italy. The first death to have occurred from the disease was reported on 27 March 2020. On 15 March, President Cyril Ramaphosa, declared a national state of disaster, and announced measures such as immediate travel restrictions and the closure of schools. The National Coronavirus Command Council was established and later the same month, 23 March, a national lockdown was announced to start on 26 March 2020. Since then, a steep rise in numbers of infected people has plagued South Africa, with many becoming infected. The global COVID-19 pandemic has had a devastating effect on South Africa. As of 04 February 2021, there have been more than 1.4 million recorded cases and 45,344 deaths. In addition, dramatic increases in hospitalizations and pressure on the health care system during the first and second waves, has led to excess deaths estimated to be at least twice as

	high as those reported. The second wave was fuelled by a variant virus, which has increased transmissibility by about 50%. Nevertheless, South African researchers and policy makers have led the way in contributing to the international COVID-19 response by conducting several vaccine trials and informing global understanding of the importance of new viral variants. These include the B.1.351 lineage that was first identified in South Africa and is now circulating inside and outside the country. The B.1.351 lineage, also known as 501Y.V2 variant and 20H/501Y.V2, is a variant of SARS-CoV-2. This variant is now appearing in almost all regions of the world where genetic surveillance of SARS-CoV-2 is being undertaken. One serious concern with this and other new variants is that they may have less sensitivity to the vaccines currently in production. *In vitro* testing has shown reductions in antibody titre of up to 4-6 fold for certain vaccines.
5.2 Overall rationale for the study summarised	The manufacturer is developing a COVID-19 vaccine based on a human replication-incompetent Ad26 vector encoding the SARS-CoV-2 S protein. The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate coronavirus vaccines against SARS-CoV (2003 outbreak), and the common conclusion that has emerged from the evaluation of several different vaccines is that the viral S protein is the only significant target for neutralizing antibodies and the only viral protein that can elicit protective immunity in animal models. Based on these findings, the S protein was selected as the sponsor's candidate vaccine antigen. Vaccine-associated enhanced disease has been described in some animal models for SARS and MERS in which candidate vaccines induced a Th2 biased immune response but proof of human SARS- or MERS-vaccine-associated enhanced disease does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. The Ad26 vector was chosen due to its ability to induce humoral and strong cellular responses with a Th1 immune phenotype. This type 1 polarity of the immune response is thought to minimize the risk of enhanced disease after SARS-CoV-2 infection.
5.3 Rationale for the study in the South African context	HCW provide essential services, particularly with regard to the COVID-19 pandemic. As frontline workers they risk daily exposure to SARS-CoV-2. Despite the extensive use of non-pharmaceutical interventions, such as personal protective equipment (PPE), HCW continue to contract SARS-CoV-2, with a number of HCW developing severe disease resulting in hospitalisation or death. Even HCW who remain asymptomatic or only develop mild disease are forced to

	isolate – this has exacerbated staff shortages and undermined the ability of the health sector to respond to the high demand for hospital based care due to the ongoing pandemic. The South African Government Covid-19 Vaccination Strategy has already prioritised the vaccination of HCW in phase 1 of the vaccine rollout, underscoring the national agreement that HCW constitute a priority group. The proposed study will be conducted in collaboration with the National Department of Health. Implementation lessons learnt with vaccine rollout to HCW will be used to inform vaccine rollout to the public in subsequent phases.

PART 6: STUDY OBJECTIVES AND ENDPOINTS (with justifications)	
6.1 Primary objectives and endpoints	Overall aim: To monitor the effectiveness of the single dose Ad26.COV2.S COVID-19 vaccine among health care workers as compared to the general unvaccinated population in South Africasub-grou Primary Objective To monitor hospitalizations or deaths in the cohort of HCWs Endpoint Rates of hospitalizations and deaths
6.2 Secondary objectives and endpoints	Secondary Objective To estimate the incidence of Symptomatic SARS CoV-2 infections among vaccinated HCWs Endpoint Incidence rate of SARS CoV-2 infection as indicated by self-report and validation in national laboratory records. Rates of severe disease in HCW who are found to be RT-PCR positive at up to 2 years post vaccination Secondary Objective To monitor the genetic diversity of breakthrough SARS CoV-2 infections Endpoint Genetic diversity of breakthrough infection virus as determined by whole genome sequencing. This will be recovered from national laboratories. Secondary Objective To measure serum neutralization and T-cell responses among vaccinees (estimated sub-set of 10,000) Endpoint Neutralization titres and Elispot assays among vaccinees

	Secondary Objective To monitor for asymptomatic infection in a sub-set of HCWs Endpoint Rates of hospitalizations and deaths Secondary Objective To monitor for asymptomatic and in a sub-set of HCWs Endpoint Rates of asymptomatic infection at baseline and follow up using SARS CoV-2 virus and antibody testing. Secondary Objective To estimate vaccine uptake among HCWs in South Africa Endpoint Proportion of HCWs approached for study participation taking part in the study and receiving the vaccine
6.3 Exploratory objectives and endpoints	Exploratory Objective To establish a link between the national pharmacovigilance system to assist with monitoring safety and any unexpected adverse effects Endpoint Numbers of safety events and/or unexpected adverse effects reported to the study team Monitor pregnancies and pregnancy outcomes reported to safety desk.
6.4 Safety objectives and endpoints	See above endpoints
6.5 Other objectives	Not Applicable

PART 7: STUDY DESIGN AND METHODOLOGY	
7.1 Study Design (with justifications) • phase of trial • choice of design • use of placebo (if applicable) • dosages • randomisation • blinding	• phase of trial: 3B • choice of design: open label, single-arm • use of placebo (if applicable): not applicable • dosages • randomisation: not applicable • blinding: not applicable • placebo: not applicable This is multi-center open-label, single-arm phase 3B implementation study in HCW in South Africa at least 18 years of age. This study will be conducted from Ensemble sites in collaboration (where appropriate) with the vaccination centers in South Africa and all HCW who register on the National Vaccination Registry will be eligible for enrolment. Participants will be scheduled using the registry and will be scheduled to receive the vaccine. Vaccination will

	be overseen by trained personnel linked to ENSEMBLE trial. Participants will receive a single dose of vaccine at enrolment; to monitor outcomes the DATCOV surveillance system and NICD line list will be reviewed for up to 2 years post-vaccination.A sub-group will be followed up for 6 months, which will also have outcomes monitored for up to a further 18 months. If a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted. The end-of-study will be considered as at least 6 months of follow up for the last participant enrolled in the study. Participants will receive intramuscular (IM) injection of Ad26.COV2.S at enrolment at a dose level of 5×10^{10} vp. Surveillance for effectiveness may continue for up to 2 years post vaccination
7.2 Duration of the study	Participants will receive a single dose of vaccine at enrolment; to monitor outcomes the DATCOV surveillance system and NICD line list will be reviewed for up to 2 years post-vaccination. A sub-group will be followed up for 6 months
7.3 Planned start and stop date of the study	Start Date: 15 February 2021 Stop Date: 15February 2022
7.4 Participant numbers (local and worldwide) include participant numbers per site in South Africa	Health Care Workers age 18 and above working in the South African public and private health care sector. Up to (N=500 000)
7.5 Provide information indicating potential of each site to recruit required number of patients within envisaged duration of trial	All sites have successfully enrolled into the previous phase 3 ENSEMBLE study in addition to having experience with enrollment into HIV clinical trials and other disease areas. Sites are set up with both infrastructure and staffing capacity.
7.6 Provide details of pharmacogenetic, biobanking or other sub-studies planned	In a sub-sample of participants more intensive pharmacogenetic, immunogenicity and whole genome sequencing of breakthrough infections, etc. will be conducted.

PART 8: ELIGIBILITY CRITERIA (with justification for each criterion)	
8.1 Inclusion criteria	• Age 18 and older • Health care worker in the private or public service • Willingness and ability to comply with all scheduled visits, vaccination plan, laboratory tests, and other study procedures, where applicable. • Capable of giving electronic or personal signed informed consent as described in Appendix 4, which includes compliance with the requirements in this protocol.

8.2 Exclusion criteria	• Any significant acute or chronic medical condition, situation or circumstance that in the opinion of the PI/designee makes the participant unsuitable for participation in the study, or jeopardises the safety or rights of the participant • Participant known to be pregnant at time of enrolment or planning within next month. • Current participation in any other research studies that would interfere with the objectives of this study. The determination of whether participation in another study would be exclusionary for a given participant will be made by the PI/designee • History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

PART 9: DATA AND SAFETY MONITORING PLAN	
9.1 Describe and comment on Data and Safety monitoring plan (provide detailed safety and monitoring plan for the study and explain how adequate site oversight will be ensured)	Data will be collected utilizing the national vaccine registry – the Electronic Vaccination Data System (EVDS) on all participants. In a sub-group of participants assigned to more intensive monitoring of immunogenicity, data will be collected using the CAPRISA electronic record. All breakthrough infections and hospitalisations will be investigated through the DATCOV NICD hospital surveillance system. NHLS will provide data on all COVID related infections in vaccines.
9.2 Provide details of Composition, Charter and Stopping rules of the Data Safety Monitoring Committee if applicable	All data accumulated on this study will be available to Janssen, Johnson & Johnson for their phase 4 programme.
9.3 Provide details of interim analyses if planned	Not Applicable
9.4 Provide AE and SAEs definitions, reporting guidelines and causality assessments to be followed Provide details of AE's and SAEs of special interest	Safety reporting will be linked to the EVDS.

PART 10: STATISTICAL MEASURES

10.1 Provide method of Sample size determination (justification of the power of the study in relation to the outcomes measures)

Sample size

In the interim analyses of the phase 3 ENSEMBLE trial, it was shown that 468 symptomatic cases of COVID-19 were detected from 43,783 adult volunteers in the USA, Latin America and South Africa. This translates to an overall attack rate of 1.1%; approximately 0.54% and 1.59% in the intervention and placebo arm, respectively, providing a vaccine efficacy of 66% against mild to severe Covid-19. Noteworthy, these estimates were driven by the force of SARS-CoV-2 infection and will vary depending on whether there is a resurgence or not. Given that vaccine efficacy was 57% in South Africa, we assume that the incidence of symptomatic SARS CoV-2 infections in this cohort might be slightly higher than 0.5%. Based on these assumptions, an exact binomial test with a nominal 5% two-sided significance level will have >90% power to detect the difference between the null hypothesis proportion, of 0.01 (i.e., 1.0%) and the alternative proportion, of 0.007 (i.e., 0.7%) when the sample size is 11 000.

Table 3 provides scenarios for various estimates.

Table 3: Number of participants to have 90% power to detect a primary endpoint

Incidence of symptomatic SARS CoV-2 infections in the placebo arm of ENSMBLE	1.0%	1.0%	1.0%	1.3%	1.3%	1.3%	1.5%	1.5%	1.5%
Incidence of symptomatic SARS CoV-2 infections among vaccinated HCWs	0.70%	0.60%	0.50%	0.70%	0.60%	0.50%	0.70%	0.60%	0.50%
Sample Size	11000	6000	3500	3200	2103	1525	2000	1404	1200

This trial is designed such that it can generate more safety data and also identify any unexpected (i.e., rare) adverse effects of the vaccine administration, while also providing sufficient efficacy data. Therefore, a relatively large sample size is needed to detect such rare events so that more precise estimates can be obtained, and this is very critical at this stage of the vaccine life cycle.

If we target 500 000 healthcare workers, the ability of the study to detect rare safety events is shown in **Table 4**.

Table 4: Probability of observing no events, at least 1 event, or at least 2 events, for a range of estimated true event rates (N=500 000).

True event rate (%)	0 events	1+ events	2+ events
1%	<0.001	>0.99	>0.99
0.1%	<0.001	>0.99	>0.99
0.01%	<0.001	>0.99	>0.99
0.05%	<0.001	>0.99	>0.99

	These probabilities in Table 4 highlight the likelihood of the study to detect either a very low or moderate safety events. Particularly, there is a very low chance (<0.001% probability) of observing no safety events if the true event rate is 0.05% or more. Moreover, the chance of observing at least one or two events is >99% if the true event rate is 0.05% or more.
10.2 Provide Statistical method(s) and analysis of qualitative and/or quantitative measures with appropriate, clear justification	Data analyses Analyses for primary endpoint(s) and some of the secondary endpoints will be performed using SAS version 9.4 (Statistical Analysis Software, North Carolina, USA) and R statistical software. All HCWs will be included in the analyses aimed at measuring vaccine uptake. However, the incidence of symptomatic SARS-CoV-2 will be assessed on a sub-cohort of HCWs who will be randomly selected for further follow-up. All deviations to be made to the statistical considerations in this protocol will be documented in the detailed statistical analyses plan (SAP) together with a detailed analysis plan for secondary objectives. Participant demographics and baseline clinical data Demographic and clinical data of all participants enrolled in the study will be summarized using descriptive statistics. Incidence of symptomatic SARS CoV-2 infections This analysis will include HCWs from the sub-cohort at their vaccination visit. The proportion of HCWs with breakthrough infections will be reported and the confidence interval of the estimate will be calculated using the score test method. This estimate will be compared to that from the placebo arm of ENSEMBLE using one sample binomial test. Safety data (hospitalizations and/or deaths) The number and the proportion of hospitalized or died due to COVID-19 will be reported and where necessary these results will be stratified by province, age, gender and co-morbidity status.
10.3 Details of data processing • how • where • when • who	EVDS will be utilized in the data processing.

PART11: ETHICAL AND ADMINISTRATIVE ISSUES	
11.1 Justification for deviation from current SA GCP guidelines	Not Applicable
11.2 Provide details of capacity building and transformation at all sites	Refer to ENSEMBLE VAC31518COV3001 CTF 1 application.
11.3 Provide details of insurance (including title, protocol, dates, policy #, amount, local vendor)	To be provided
11.4 Provide details of indemnity for Investigators and trial site	All investigators are personally covered with medical malpractice insurance by the Medical Protection Society (MPS). This is included in the submission and filed with the applicable staff documents.
11.5 Ensure Patient Information Leaflet and Informed Consent / Assent includes: • latest ABPI and SA GCP guidelines • written in appropriate level of education/English • explains possible benefits / risks • ensuring patient rights • SAHPRA and Ethics contact names and numbers • Other details as per ICH GCP • Confirm translations available	Participant Information Sheet and Informed Consent Form Version 1.0, Dated 08 February 2021
11.6 Provide separate PILs and informed consent forms for any proposed • archiving of blood specimens for later research • genetics research • HIV testing • any other	Not Applicable
11.7 Provide details of publication policy	Open access publication policy
11.8 Provide details of remuneration and other benefits for participants	Not Applicable
11.9 Provide details of remuneration of investigators or site	The budget is in draft. A preliminary amount of R200 million is available for this study.
11.10 Provide a list of Ethics Committees which will be involved in approving the study	This application will be sent to the local ethics committees including: University of the Witwatersrand Human Research Ethics Committee (Wits HREC), Pharma-Ethics, University of Cape Town Human Research Ethics Committee (UCT HREC),

PART11: ETHICAL AND ADMINISTRATIVE ISSUES	
	South African Medical Research Council (SAMRC) Human Research Ethics Committee, University of KwaZulu-Natal Biomedical Research Ethics Committee, University of Stellenbosch Ethics Committee, Sefako Makgatho University Research Ethics Committee (SMUREC).
11.11 Provide details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial	All participating investigators completed and signed the SAHPRA declaration forms and confirmed not conflict of interest. Refer to ENSEMBLE VAC31518COV3001 CTF 1 application.
11.12 Provide updated proof of GCP training for staff involved in this trial (done in the past three years)	Proof of GCP training for all site involved in this trial has been included. Included with each site staff documents. . Refer to ENSEMBLE VAC31518COV3001 CTF 1 application.
11.13 Provide details on treatment and/or management of participants and their disease condition(s) after completion of trial (Post trial medicine access)	Not Applicable

PART 12: ADDITIONAL COMMENTS	
Provide any additional information that may be relevant to the study	Protocol approval required by 10 February 2021 in order to implement rollout strategy for the country.