Efficacy of a bivalent (D614 + B.1.351) SARS-CoV-2 Recombinant Protein Vaccine with AS03 adjuvant in adults: a Phase 3, multi-country study

Contents

1.0 Supplementary Methods

1.1 Sites participating in the study

Principal Investigator	Location	City
Colombia		
Maria Angelica Granados	Centro de Atencion e Investigacion Medica S.A.S. – Caimed S.A.S – sede Bogotá	Bogotá
Alberto Cadena Bonfanti	Clinica de la Costa	Barranquilla
Hugo Macareno Arroyo	Fundacion Hospital Universidad del Norte	Soledad
Eduardo Lopez-Medina	Centro de Estudios en Infectología Pediátrica CEIP, Department of Pediatrics Universidad del Valle and Clinica Imbanaco Grupo Quironsalud	Cali
Humberto Reynales	Centro de Atención e Investigación Médica S.A.S. – CAIMED Chía	Chía
Jaime Augusto Carrillo	Centro de Atención e Investigación Médica S.A.S.– CAIMED Girardot	Girardot
Jose Accini	IPS Centro Cientifico	Barranquilla
Hector Velásquez	Centro de Atención e Investigación Médica S.A.S. – sede Acacías	Acacias
Edith Rodriguez	Centro de Atención e investigación Médica CAIMED S.A.S	Aguazul
Erwin Pardo	Centro de Atencion e investigacion Medica CAIMED SAS	Armenia
Ghana		
Nana Akosua Ansah	Navrongo Health Research Centre (NHRC)	Navrongo
Kwaku Poku Asante	Research and Development Division, Ghana Health Service, Kintampo North Municipality	Kintampo
John Humphrey Amuasi	Kwame Nkrumah University of Science and Technology & Kumasi Center for Collaborative Research in Tropical Medicine	Kumasi
India		
Manish Jain	Maharaja Agrasen Superspeciality Hospital	Jaipur
Jinen Shah	Aartham Multi Super Speciality Hospital	Ahmedabad
Chandramani Singh	All India Institute of Medical Science (AIIMS)	Patna
Jitendra Singh Kushwaha	Prakhar Hospital Private Limited	Kanpur
Satyajit Mohapatra	SRM Medical College & Research Centre,	Chennai
Amit Suresh Bhate	Jeevan Rekha Hospital	Belagavi
Nitin Khandelwal	Vidarbha Institute of Medical Sciences	Nagpur
Veer Bahadur Singh	Jawaharlal Nehru Medical College Campus	Ajmer
Chandan Das	Institute of Medical Sciences and Sum Hospital	Bhubaneswar
Kenya		
Videlis Nduba	Kenya Medical Research Institute- Centre for Respiratory Disease Research	Nairobi
Lucas Otieno Tina	Kenya Medical Research Institute (KEMRI)/USAMRD-Africa/Kenya	Kisumu
Samuel Gurrion Ouma	Kenya Medical Research Institute CGHR, HIVR Division	Kisumu
Fredrick Sawe	Kenya Medical Research Institute – US Army Medical Research	Kericho
Abraham Siika	Moi University CRC	Eldoret
Mansoor Saleh	Aga Khan University Hospital	Nairobi
Kishorchandra Mandaliya	Ganjoni Clinic	Mombasa
Nelly Mugo	Kenya Medical Research Institute – Partners in Health Research & Development	Thika
Janet Oyieko	Kenya Medical Research Institute – Butere County Hospital	Butere
Elisabeth Bukusi	Kenya Medical Research Institute – Centre for Microbiological Research, Research Care and Training Program	Kisumu
Mexico		
Luis Espinoza	Arke SMO SA de CV	Veracruz

Maria Otero	Hospital Civil "Fray Antonio Alcalde"	Guadalajara
Rafael Rivero	Centro de Investigación Clínica del Pacífico S.A. de C.V.	Acapulco
Javier Martínez	Morales Vargas Centro de investigación	León
Sandra Villagómez-Martínez	Hospital General de Temixco, en acuerdo con el Instituto Nacional de Pediatría Unidad de Apoyo a la Investigación Clínica.	Temixco
Mercedes Paredes	JM Research SC	Cuernavaca
Pedro Sánchez	Instituto Nacional de Pediatría	Coyoacán
Nepal		
Piush Kanodia	Nepalgunj Medical college Teaching Hospital	Nepalgunj
Dipesh Tamrakar	Dhulikhel Hospital, Kathmandu University Hospital	Dhulikhel
Santa Kumar Das	Institute of Medicine, Tribhuvan University	Kathmandu
Uganda		
Patricia Nahirya Ntege	Baylor College of Medicine Children's Foundation-Uganda	Kampala
Brenda Okech	Uganda Virus Research Institute (UVRI)-IAVI HIV Vaccine Program LTD. CRS	Entebbe
Hannah Kibuuka	Makerere University Walter Reed Project	Kampala
Cissy Kityo Mutuluuza	Joint Clinical Research Centre	Kampala
Anne Wajja	Medical Research Council/Uganda Virus Research Institute/London School of Hygiene and Tropical Medicine Uganda Research Unit	Entebbe
Deo Wabwire	MUJHU Research Collaboration / MUJHU Care Ltd	Kampala
Noah Kiwanuka	Africa Medical And Behavioural Sciences Organisation, Nansana	Waikso
Francis Kiweewa	Strengthening Institutional Capacity for Research Administration at Lira Regional Hospital	Lira
Ukraine		
Svitlana Postol	Synexus Affiliate - MC of LLC Medbud-Clinic	Kyiv
Hanna Beyko	Center of Family Medicine Plus LLC	Kyiv
Oleksandra Bilotkach	AES - AS - Medical Center of Edelweiss Medics LLC	Kyiv
Dmytro Dobryanskyi	Medical Center Medical Clinic Blagomed LLC	Kyiv

1.2 Local and regional institutional ethics committees

Colombia: Comité de Ética en Investigación CAIMED (approved); Comité de Ética en Investigación de la Fundación del Caribe para la Investigación Biomédica (approved); Comité de Ética en Investigación VITA (approved); Corporación Científica Pediátrica Comité de Etica en Investigación Biomédica (approved); Comité de Ética en investigación de la División Ciencias de la Salud de la Universidad del Norte (approved); Comité de Ética en Investigación Clínica de la Costa (approved). **Ghana**: Kwame Nkrumah University of Science and Technology Committee on Human Research, Publication and Ethics (approved); Kintampo Health Research Centre Institutional Ethics Committee (approved); Navrongo Health Research Centre Institutional Review Board (approved); Ghana Health Service Ethics Review Committee (approved). **India**: Institute of Medical Sciences and Sum Hospital Institutional Ethics Committee (approved); Jawahar Lal Nehru Medical College Institutional Ethics Committee (approved); Vidharba Institute of Medical Sciences - Nagpur Institutional Ethics Committee (approved); Jeevan Rekha Hospital Institutional Ethics Committee (approved); SRM Medical College Hospital and Research Centre Institutional Ethics Committee (approved); Prakhar Hospital Institutional Ethics Committee (approved); All India Institute of Medical Sciences Patna Institutional Ethics Committee (approved); Aartham Ethics Committee - Aartham Multi Super Speciality Hospital (approved); Maharaja Agrasen Superspeciality Hospital Institutional Ethics Committee (approved). **Kenya**: Kenya Medical Research Scientific & Institute Ethics Review Unit (approved); Kenyatta National Hospital - University of Nairobi - College of Health Sciences Ethics Review Committee (approved); The Aga Khan University - Nairobi Institutional Ethics Review Committee (approved); Institutional Review Ethics Committee MOI University College of Health - MOI Teaching and Referral Hospital (approved); National Commission for Science Technology and Innovation (approved). **Mexico**: Comité de Ética en Investigación de la Dirección de Investigación del Instituto Nacional de Pediatría; Comité de Ética en Investigación de Médica Sur (approved); Comité de Ética en Investigación Hospital Aranda de la Parra (approved); Comité de Ética en Investigación Hospital Civil de Guadalajara - Sub-Dirección de Enseñanza e Investigación (approved); Comité de Ética en Investigación de Investigación Biomédica para el Desarrollo de Fármacos (approved). **Nepal**: Tribhuvan University Institute of Medicine Institutional Review Committee (approved); Kathmandu University School of Medical Sciences Institutional Review Board (approved); Nepalgunj Medical College Teaching Hospital Institutional Review Committee (approved). **Uganda**: Uganda Virus Research Institute (approved); London School of Hygiene and Tropical Medicine Research Ethics Committee (approved). **Ukraine**: Blagomed Medical Clinic LLC Ethics Commission (approved); Edelweiss Medics LLC (approved); Center of Family Medicine Plus LLC Ethical Committee (approved); Medbud Clinic LLC Ethical Committee (approved).

1.3 Participant inclusion/exclusion criteria

Patients are eligible for the study only if all the following criteria are met:

- Aged ≥18 years on the day of inclusion
- No intention to receive an authorized/approved COVID-19 vaccine outside of the study
- SARS-CoV-2 rapid serodiagnostic test performed at the time of enrolment to detect presence of SARS-CoV-2 antibodies
- For persons living with HIV, their HIV infection must be stable as determined by ongoing anti-retroviral treatment and a CD4 cell count of >200 cells/mm^3
- Females of childbearing potential must agree to use an effective contraceptive method or remain abstinent from ≥4 weeks prior to the first study intervention administration until ≥12 weeks after the second study intervention administration; have a negative highly sensitive pregnancy test ≤25 hours before any dose of study intervention
- Females of non-childbearing potential must be post-menopausal for ≥1 year or surgically sterile
- Provision of a signed and dated written informed consent form
- Able to attend all visits and to comply with all study procedures
- Covered by health insurance, if required by local, regional or national regulations

Participants are not eligible for the study if any of the following criteria are met:

- Known systemic hypersensitivity to any of the vaccine components or a history of a life-threatening reaction to a vaccine containing any of the same substances
- Dementia or any other cognitive condition at a stage that could interfere with following the study procedures based on Investigator's judgement
- Self-reported thrombocytopenia, contraindicating intramuscular vaccination based on Investigator's judgement
- Bleeding disorder or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating intramuscular vaccination based on Investigator's judgement
- Unstable acute or chronic illness that in the opinion of the Investigator or designee poses additional risk as a result of participation or that could interfere with the study procedures
- Moderate or severe acute illness/infection (according to investigator judgement) on the day of vaccination or febrile illness (temperature ≥38°C [≥100·4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided
- Receipt of any vaccine in the 30 days preceding or on the day of the first study vaccination or planned receipt of any vaccine between the first study vaccination and in the 30 days following the second study vaccination except for influenza vaccination, which may be received at any time in relation to study intervention
- Prior administration of a coronavirus vaccine (SARS-CoV-2, SARS-CoV, MERS-CoV)
- Receipt of solid-organ or bone marrow transplants in the past 180 days
- Receipt of anti-cancer chemotherapy in the last 90 days
- Participation at the time of study enrolment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device or medical procedure
- Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
- Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e. parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

1.4 Participants potentially at higher risk of severe COVID-19

High-risk conditions are conditions considered to be associated with an increased risk of severe COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html) and include:

- cancer
- chronic kidney disease
- chronic obstructive pulmonary disease (COPD)
- immunocompromised state from solid organ transplant
- immunocompromised state from other causes (blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of immunosuppressors)
- obesity (body mass index of ≥30)
- heart conditions such as heart failure
- coronary artery disease or cardiomyopathies
- sickle cell disease
- thalassemia
- type 1 or type 2 diabetes mellitus
- moderate-to-severe asthma
- cerebrovascular disease
- cystic fibrosis
- hypertension/high blood pressure
- neurologic conditions
- hepatic disease
- pulmonary fibrosis
- smoking

1.5 Definition of COVID-19 like illness

New onset or exacerbation of any ONE of the following:

- Fever (measured temperature ≥ 100·4ºF OR ≥ 38·0ºC)
- Difficulty breathing or shortness of breath
- Altered level of consciousness
- Myocarditis, myocardial infarction
- Thromboembolic event (blood clots [eg, pulmonary embolism, deep vein thrombosis, stroke])
- Purpura fulminans
- Clinical or radiographic evidence of pneumonia
- Chilblains (COVID-toes)

OR

New onset or exacerbation of ANY ONE of the following (that persists for a period of at least 24 hours or reoccurs after a 12-hour period):

- Cough (dry or productive)
- Anosmia or partial loss of smell
- Ageusia or dysgeusia (loss or disturbance of taste)

OR

New onset of any TWO of the following symptoms that are present at the same time (both symptoms that persist for a period of at least 24 hours or reoccur after a 12-hour period):

- Sore throat
- Chills
- Myalgia
- Fatigue
- Malaise
- Headache
- Rhinorrhea or nasal congestion
- Abdominal pain
- At least one of nausea, diarrhea, vomiting

1.6 Testing procedures and criteria for determination of prior SARS-CoV-2 infection

Participants were classified as naïve or non-naive at Day 1 and Day 22 or Day 1 or Day 22 by assessment of blood samples using Elecsys electrochemiluminescence immunoassays for detection of anti-S antibodies (Elecsys Anti-SARS-CoV-2 S assay; Roche, Indianapolis, IN, USA) on study Day 1 and for detection of anti-nucleocapsid antibodies (Elecsys Anti- SARS-CoV-2 N; Roche) on study Days 1 and 22; and detection of SARS-CoV-2 nucleic acids in nasopharyngeal swabs using nucleic-acid amplification tests (NAAT; Abbott RealTime SARS-CoV-2 assay; Abbott Molecular, Des Plaines, IL, USA) on study Days 1 and 22. Analyses were done according to the manufacturers' instructions. Participants were defined as naive to SARS-CoV-2 on study Days 1 and 22 if they tested negative for anti-S antibodies on study Day 1 and for both anti-nucleocapsid antibodies and SARS-CoV-2 nucleic acids on Days 1 and 22; we defined participants as non-naive if they tested positive on at least one of the three tests on study Days 1, 22, or both.

The prior SARS-CoV-2 infection status of all randomized participants were defined in accordance with the below criteria.

Prior SARs-CoV-2 infection status	**Description**
SARS-CoV-2 Naïve at baseline (Naïve-D1)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by the anti-N immunoassay on D01 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Non-Naïve at baseline (Non-Naïve-D1)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 serum sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Naïve at second injection (Naïve-D1+D22)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by anti-N immunoassay on D01 and D22 serum samples AND • Negative NAAT for SARS-CoV-2 on respiratory samples collected on D01 and D22
SARS-CoV-2 Non-Naïve at second injection (Non-Naïve - D1/D22)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 or D22 serum samples OR • Positive NAAT for SARS-CoV-2 on respiratory samples collected on D01 or D22

1.7 Definition of COVID-19 efficacy outcomes

Virologically confirmed SARS-CoV-2 infection

Defined as a positive result for SARS CoV-2 by NAAT on at least one respiratory sample. This includes positive results by any NAAT including tests performed outside the study protocol if confirmed by the adjudication committee.

Symptomatic COVID-19

Defined as virologically confirmed SARS-CoV-2 infection accompanied by protocol-defined COVID-19-like illness.

Asymptomatic SARS-CoV-2 infection

Defined as SARS-CoV-2 infection, with no reported COVID-19-like illness episodes between enrolment and 14 days after the timepoint at which SARS-CoV-2 infection is ascertained, based on samples taken during previous visits.

Hospitalized COVID-19

Defined as an episode of Symptomatic COVID-19 that requires inpatient hospitalization.

Moderate COVID-19

Defined as Symptomatic COVID-19 with:

- Shortness of breath that persists for at least 12 hours

OR

- Clinical signs of moderate illness measured at least on two occasions separated by 30 mins (respiratory rate [RR] ≥ 20 breaths per minute at rest AND heart rate [HR] ≥ 90 beats per minute at rest)

AND

- No clinical signs indicative of severe COVID-19

Severe COVID-19: defined as COVID-19 with any one of the following:

- Any clinical signs of severe illness measured at least on 2 occasions separated by 30 minutes (saturation of oxygen [SpO2] ≤ 93% on room air (corrected for altitude), PaO2/FiO2 < 300 mm Hg, RR ≥ 30 breaths per minute at rest, HR ≥ 125 beats per minute at rest)
- Supplemental oxygen administration for > 1 hour
- Use of invasive or non-invasive ventilation or Extracorporeal Membrane Oxygenation
- Clinical diagnosis of respiratory failure (ie, clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- Significant acute renal, hepatic, or neurologic dysfunction
- Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
- Admission to an ICU
- Death

COVID-19 severity scale

The COVID-19 severity scale is based on the ordinal scale of clinical assessment:

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen

5. Hospitalized, not requiring supplemental oxygen – discharged but requiring ongoing medical care (COVID-19 related or otherwise)

6. Hospitalized, not requiring supplemental oxygen – discharged without ongoing medical care

7. Not hospitalized

Death associated with COVID-19

Death associated with COVID-19 is defined as death in a participant with COVID-19 who died within 28 days of the first positive specimen date if association confirmed by adjudication committee OR died more than 28 days after the first specimen date and COVID-19 is mentioned as an immediate or underlying cause of death on the death certificate if association confirmed by the adjudication committee.

1.8 Safety data

Safety data included all immediate unsolicited systemic AEs within 30 minutes of each injection, medically attended AEs (MAAEs), serious AEs (SAEs), AEs of special interest (AESIs) including potential immune-mediated diseases (pIMDs).

AESIs included:

- Anaphylactic reactions
- Generalized convulsion
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Myocarditis
- Pericarditis
- New onset and worsening of potential immune-mediated diseases

1.9 Sample size calculations

It was estimated that a sample of 10,886 participants would be required, with approximately 125 symptomatic COVID-19 cases needed to achieve 80% statistical power. Participants were enrolled and randomized with allocation ratio (1:1) into the vaccine group and the placebo group. Among those, the planned target for SARS-CoV-2 non-naïve participants was approximately 3,266 participants (1,633 per arm). The sample size of 7,620 SARS-CoV-2 naïve participants was powered independently to demonstrate the primary objective of vaccine efficacy (VE) against symptomatic COVID-19 in SARS-CoV-2 naïve adults; however, only 1,176 were naïve at D1. Of note, the primary endpoint, including both naïve and non-naïve participants, was changed after enrollment was already completed; therefore, sample size calculations were based on a primary endpoint that considered only naïve participants. The power of primary efficacy analysis is driven by the total number of symptomatic COVID-19 events.

The incidence rate of symptomatic COVID-19 in Placebo is assumed as 2·25% illness rate per 2-months follow-up period. An attrition rate of 30% was expected, as, during the conduct of the study, a greater proportion of the cohort became eligible to receive locally available authorized COVID-19 vaccines.

The power of primary efficacy analysis was driven by the total number of symptomatic COVID-19 events. Because Omicron was the prevalent variant during case accrual for Stage 2 and the expected VE against Omicron was expected to be lower than the original assumption of 70%,[1] the expected true VE for symptomatic COVID-19 for Stage 2 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events was required to achieve 80% power with one-sided type I error rate of 0·025, assuming no interim analysis. For interim analyses, type I error rate was adjusted appropriately. If the planned interim analysis was skipped, or if the information fraction is different than planned (not within the range of 50% to 70% data), alpha splitting was adjusted based on the Lan-DeMets O'Brien-Fleming approximation spending function approach for interim and final efficacy analysis, if applicable.

For the primary endpoint, the confidence intervals (CI) corresponding to vaccine efficacy estimates were calculated by an exact method,[2] assuming a binomial distribution of the number of cases in the vaccine group, conditional to the total number of cases.

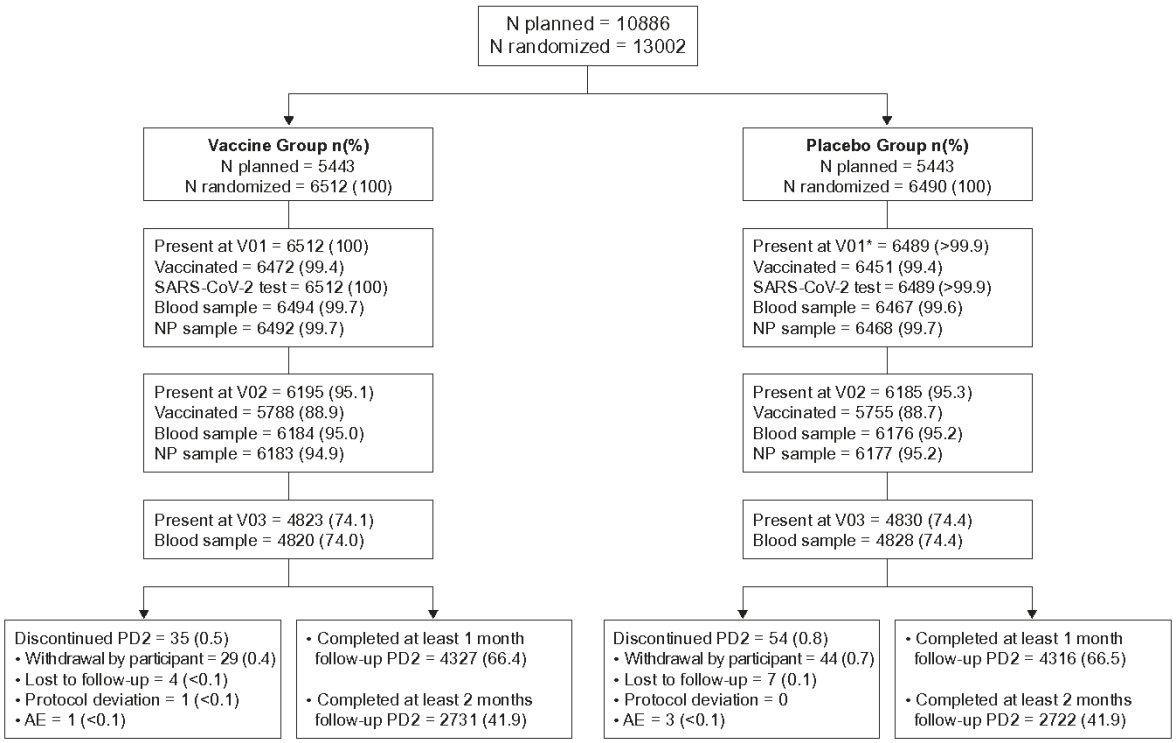
For other analyses, an unadjusted 95% CI was calculated.

1.10 Descriptions of the analysis sets

Population	Description
Screened	All participants screened for potential study enrolment will be included regardless of being enrolled or not being enrolled. The screening includes the SARS-CoV-2 rapid serodiagnosis test results, demographic information (age, ethnic/racial population, high-risk medical conditions), and inclusion/exclusion criteria. The participants reaching the enrolment cap identified in interactive response technology will be excluded from the study enrolment and will have no participant ID assigned.
Randomized	All participants with a randomized group that has been allocated by IRT
Full analysis set (FAS)	All randomized participants who receive at least one study injection. Participants will be analyzed according to the intervention to which they were randomized
Safety Analysis Set (SafAS)	All randomized participants who have received at least one dose of the study vaccine or placebo and with documented safety data. All participants will have their safety analysed after each dose according to the intervention they actually received, and after any dose according to the intervention received at the first dose. Safety data recorded for participants not administered a study intervention will be excluded from the analysis (and listed separately).
Reactogenicity Safety Analysis Subset (RsafAS)	Subset of the SafAS and comprising all participants who receive at least one study injection and are randomized into the reactogenicity subset and who have reported reactogenicity data.
Modified Full Analysis Set post-dose 1 (mFAS-PD1)	Subset of the FAS excluding: • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and 14 days after the first injection • Participant discontinued from study before 14 days after the first injection
Modified Full Analysis Set post-dose 2 (mFAS-PD2)	Subset of the FAS excluding: • Participants who did not complete the vaccination schedule (2 injections) • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and before 14 days after the second injection • Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant discontinued from study before 14 days after the second injection

2.0 Supplementary efficacy data

2.1 CONSORT diagram for participant flow through the study



Data are presented as number (%). *V1 for one participant did not appear in the database during the data extraction dated 09 June 2022 because the site was entering additional data for V01 at the time the data extraction was performed. However, this participant was included in mFAS-PD1, mFAS-PD2, mFAS-PD2 Non-naïve-D01/D22 analysis sets because both V01 and V02 were performed. Abbreviations: AE, adverse event. NP, nasopharyngeal. PD2, post dose 2. V, visit.

2.2 Reasons for discontinuation

	Vaccine group (N=6512)	Placebo group (N=6490)	All (N=13002)
Overall (n=414)			
Adverse event*, n (%)	4 (<0·1)	5 (<0·1)	9 (<0·1)
Protocol deviation, n (%)	26 (0·4)	23 (0·4)	49 (0·4)
Withdrawal by subject, n (%)	146 (2·2)	160 (2·2)	306 (2·4)
Lost to follow-up, n (%)	26 (0·4)	24 (0·4)	50 (0·4)
Discontinued after second injection (n=89)			
Adverse event*, n (%)	1 (<0·1)	3 (<0·1)	4 (<0·1)
Protocol deviation, n (%)	1 (<0·1)	0	1 (<0·1)
Withdrawal by subject, n (%)	29 (0·4)	44 (0·7)	73 (0·6)
Lost to follow-up, n (%)	4 (<0·1)	7 (0·1)	11 (<0·1)

*All adverse events were assessed as unrelated to the study intervention.

2.3 Main analysis sets by age group, prior SARS-CoV-2 infection at baseline, and presence of high-risk medical conditions

		Vaccine group (N=6,512) n	Placebo group (N=6,490) n
Overall	FAS	6,472	6,452
	mFAS-PD2	5,736	5,680
	SafAS	6,472	6,450
	RSafAS	2,433	2,418
18–59 years	FAS	6,078	6,069
	mFAS-PD2	5,404	5,350
	SafAS	6,078	6,067
	RsafAS	2,040	2,037
≥60 years	FAS	394	383
	mFAS-PD2	332	330
	SafAS	394	383
	RsafAS	393	381
Naïve at D1	FAS	588	588
	mFAS-PD1	577	576
	SafAS	588	588
	RsafAS	332	347
Non-naïve at D1	FAS	4,860	4,833
	mFAS-PD1	4,826	4,793
	SafAS*	4,860	4,831
	RsafAS	1,835	1,802
Naïve at D1 and D22	FAS	333	350
	mFAS-PD2	327	343
Non-naïve at D1 or D22	FAS	5,478	5,488
	mFAS-PD2	4,841	4,818
Presence of high-risk medical conditions	FAS	2,095	2,070
	mFAS-PD2	1,793	1,786
	SafAS	2,095	2,070
	RsafAS	869	862
No presence of high-risk medical conditions	FAS	4,377	4,382
	mFAS-PD2	3,943	3,894
	SafAS	4,377	4,380
	RsafAS	1,564	1,556

N=number of randomised participants.

Abbreviations: FAS, Full analysis set; mFAS-PD1, modified full analysis set post-dose 1; mFAS-PD2, modified full analysis set post-dose 2; RsafAS, reactogenicity safety analysis set; SafAS, safety analysis set.

*The product received by two participants (i.e. vaccine or placebo) could not be determined; therefore, there is a difference of two participants between the FAS and the SafAS; the same difference is observed between the FAS and SafAS post-dose 1.

2.4 High risk medical conditions - SafAS

	Vaccine group (N=6,472) n (%)	Placebo group (N=6,450) n (%)	Total (N=12,924) n (%)
No	4377 (67·6)	4380 (67·9)	8759 (67·8)
At least one high-risk medical condition	2095 (32·4)	2070 (32·1)	4165 (32·2)
Smoking	1068 (16·5)	1040 (16·1)	2108 (16·3)
Obesity (body mass index of 30 or higher)	616 (9·5)	580 (9·0)	1196 (9·3)
Immunocompromised State from Other Causes	323 (5·0)	342 (5·3)	665 (5·1)
Hypertension / High Blood Pressure	281 (4·3)	309 (4·8)	590 (4·6)
Type 2 Diabetes Mellitus	92 (1·4)	84 (1·3)	176 (1·4)
Moderate to Severe Asthma	24 (0·4)	22 (0·3)	46 (0·4)
Chronic Kidney Disease	11 (0·2)	9 (0·1)	20 (0·2)
Hepatic Disease	11 (0·2)	7 (0·1)	18 (0·1)
Neurologic Conditions	10 (0·2)	8 (0·1)	18 (0·1)
Type 1 Diabetes Mellitus	8 (0·1)	9 (0·1)	17 (0·1)
Cardiovascular Disorder / Heart Failure	7 (0·1)	9 (0·1)	16 (0·1)
Cancer	7 (0·1)	4 (<0·1)	11 (<0·1)
Coronary Artery Disease or Cardiomyopathies	8 (0·1)	3 (<0·1)	11 (<0·1)
Chronic Obstructive Pulmonary Disease	6 (<0·1)	4 (<0·1)	10 (<0·1)
Immunocompromised State from Solid Organ Transplantation	4 (<0·1)	1 (<0·1)	5 (<0·1)
Sickle Cell Disease	3 (<0·1)	0	3 (<0·1)

SafAS, safety analysis set.

2.5 Follow-up data – SafAS (PD1)

	Vaccine group	Placebo group	Total
All			
Follow-up duration,* days	148	148	148
Median subject follow-up duration,† days	85	85	85
Total follow-up duration,‡ 1000-person years	1·335	1·335	··
Aged 18–25 years			
Follow-up duration,* days	147	148	148
Median subject follow-up duration,† days	79	83	82
Total follow-up duration,‡ 1000-person years	0·320	0·322	··
Aged 18–59 years			
Follow-up duration,* days	148	148	148
Median subject follow-up duration,† days	85	85	85
Total follow-up duration,‡ 1000-person years	1·256	1·259	··
Aged ≥60 years			
Follow-up duration,* days	124	125	125
Median subject follow-up duration,† days	76	71	72
Total follow-up duration,‡ 1000-person years	0·079	0·076	··
Aged 18–64 years			
Follow-up duration,* days	148	148	148
Median subject follow-up duration,† days	85	85	85
Total follow-up duration,‡ 1000-person years	1·300	1·296	··
Aged ≥65 years			
Follow-up duration,* days	124	124	124
Median subject follow-up duration,† days	76	76	76
Total follow-up duration,‡ 1000-person years	0·034	0·039	··

*Follow-up duration: data cut-off date – minimum of all SafAS subjects (Visit 01 date) + 1.
†Subject follow-up duration: minimum (data cut-off date, termination date or death date) – Visit 01 date + 1.
‡Total study follow-up duration: sum of subject follow-up duration / (365·25 * 1000)

PD1. Post dose 1; SafAS, safety analysis set.

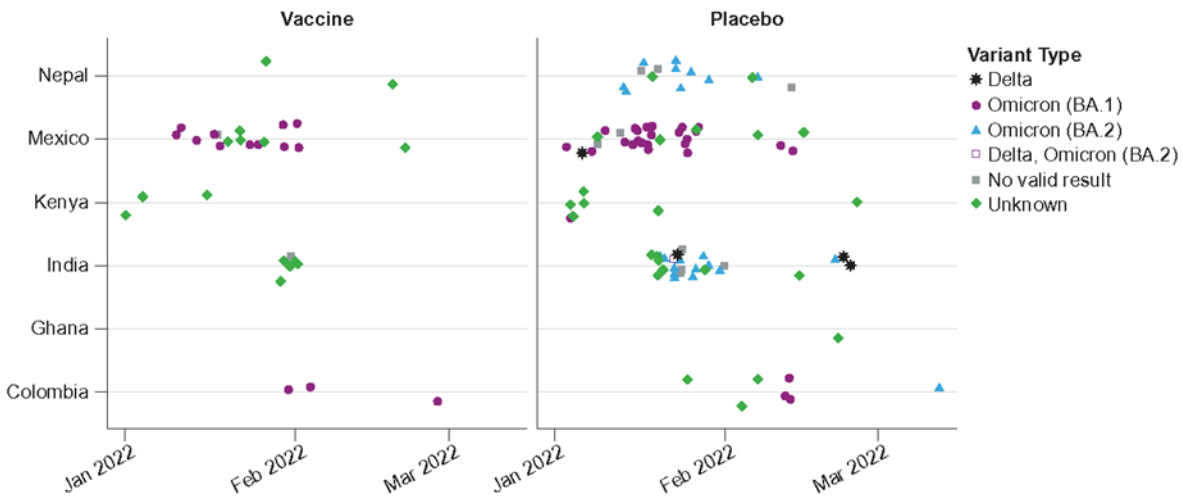
2.6 Follow-up data – mFAS-PD2

	Vaccine group	Placebo group	Total
All			
Follow-up duration,* days	118	118	118
Median subject follow-up duration,† days	58	58	58
Total follow-up duration,‡ 1000-person years	0·824	0·818	··
Aged 18–25 years			
Follow-up duration,* days	117	118	118
Median subject follow-up duration,† days	56	57	56
Total follow-up duration,‡ 1000-person years	0·191	0·192	··
Aged 18–59 years			
Follow-up duration,* days	118	118	118
Median subject follow-up duration,† days	58	58	58
Total follow-up duration,‡ 1000-person years	0·779	0·773	··
Aged ≥60 years			
Follow-up duration,* days	100	104	104
Median subject follow-up duration,† days	54	50	51
Total follow-up duration,‡ 1000-person years	0·045	0·045	··
Aged 18–64 years			
Follow-up duration,* days	118	118	118
Median subject follow-up duration,† days	58	58	58
Total follow-up duration,‡ 1000-person years	0·803	0·795	··
Aged ≥65 years			
Follow-up duration,* days	100	100	100
Median subject follow-up duration,† days	56	51	55
Total follow-up duration,‡ 1000-person years	0·021	0·023	··

*Follow-up duration: Data cut-off date - Minimum of all mFAS-PD2 subjects (date of V02) + 1. †Subject follow-up duration: Minimum (data cut-off date, termination date, or death date) - V02 date + 1. ‡Total follow-up duration: Sum of subject follow-up duration / (365·25 * 1000)

mFAS-PD2, modified full analysis set post-dose 2.

2.7 Variant distribution by country and calendar time in all participants, regardless of prior SARS-CoV-2 infections (mFAS-PD2)

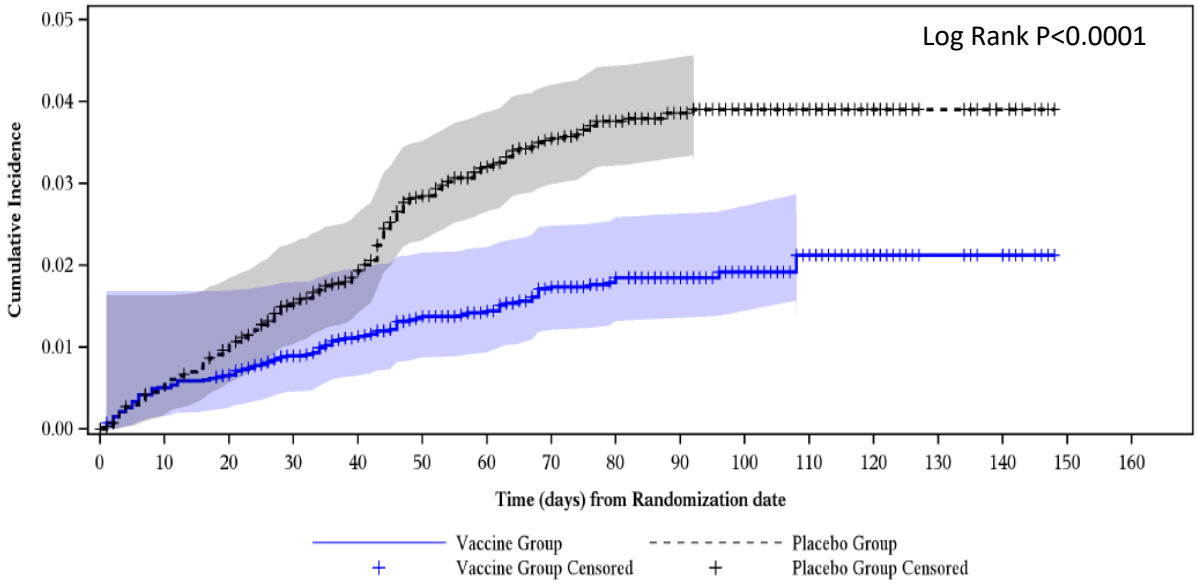


2.8 Vaccine efficacy - Sensitivity analysis including Ukrainian participants

	Vaccine group (N=5876)			Placebo group (N=5802)			Vaccine efficacy	
	Cases	1000 person years at risk	Incidence rate (95% CI)	Cases	1000 person years at risk	Incidence rate (95% CI)	%	95% CI
Symptomatic COVID-19	33	0·609	54·22 (37·32; 76·14)	90	0·597	150·75 (121·22; 185·30)	64·0	(45·9; 76·6)

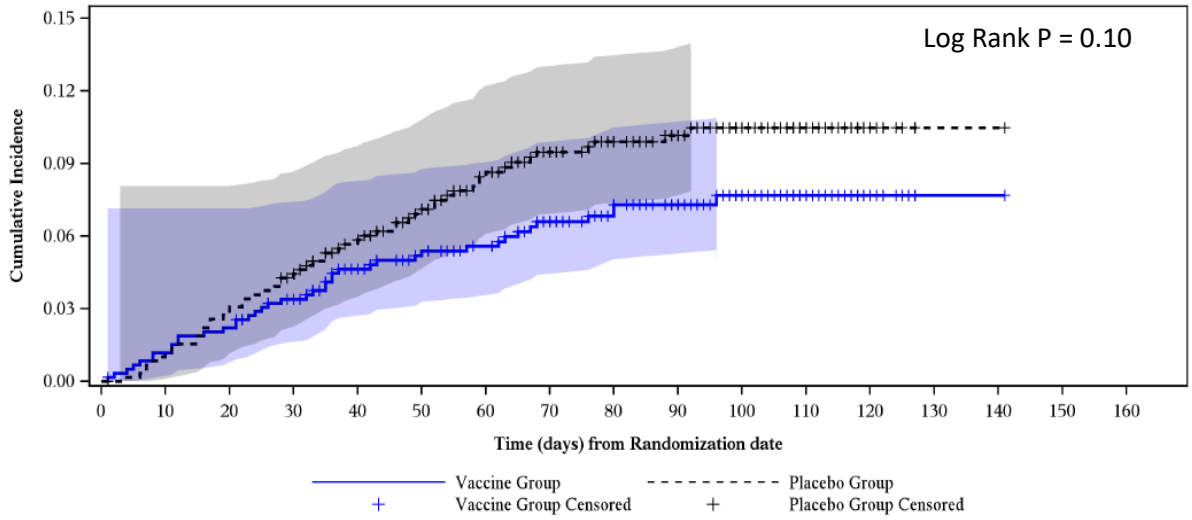
Cases: number of subjects with ≥1 occurrence of relevant endpoint from 14 days post-injection 1 in the analysis population.CI, confidence interval.

2.9 Kaplan-Meier cumulative incidence of symptomatic COVID-19 in the randomized population (overall, naïve and non-naïve populations) from randomisation A. Randomized (all)



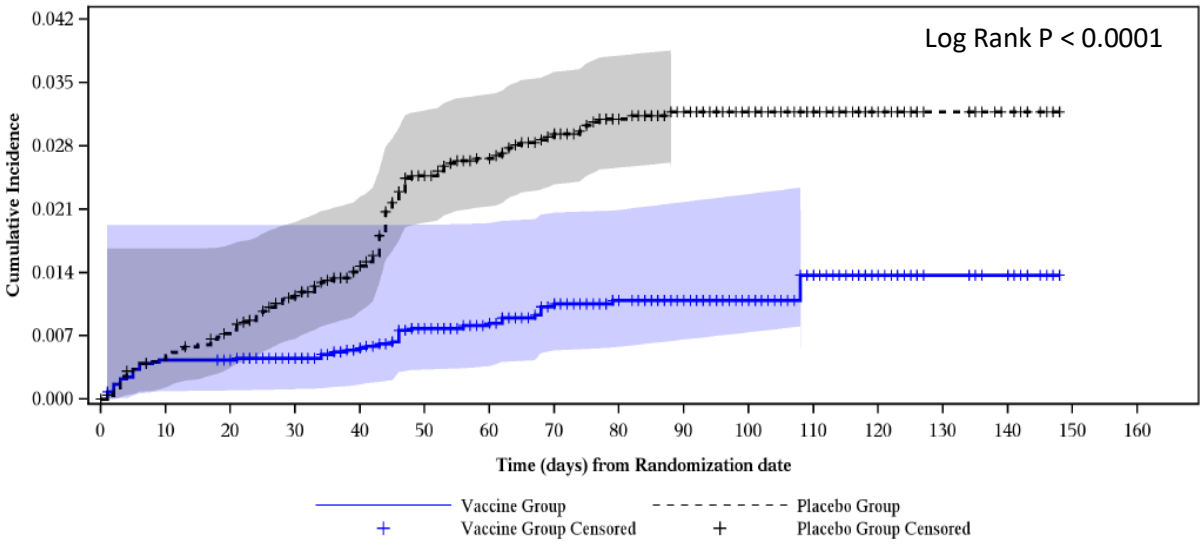
	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	148
Number at risk (censored)																
Vaccine	6512 (0)	6429 (50)	6417 (53)	6346 (108)	5715 (726)	4786 (1642)	4262 (2163)	3847 (2566)	3443 (2967)	2466 (3942)	858 (5549)	454 (5952)	158 (6248)	23 (6383)	19 (6387)	0 (6406)
Placebo	6490 (0)	6406 (53)	6371 (57)	6292 (101)	5658 (714)	4719 (1600)	4186 (2117)	3781 (2508)	3372 (2908)	2391 (3882)	841 (5435)	441 (5835)	152 (6124)	23 (6250)	18 (6258)	0 (6276)
Cumulative events																
Vaccine	0	33	43	58	72	85	88	100	104	104	105	106	106	106	106	106
Placebo	0	35	66	99	123	172	188	202	210	213	214	214	214	214	214	214
Estimate (95% CI)																
Vaccine	0	0.005 (0.002; 0.017)	0.007 (0.003; 0.017)	0.009 (0.004; 0.018)	0.011 (0.007; 0.020)	0.014 (0.009; 0.022)	0.014 (0.009; 0.022)	0.017 (0.012; 0.025)	0.018 (0.013; 0.026)	0.018 (0.013; 0.026)	0.019 (0.014; 0.027)	0.021 (0.016; 0.029)	0.021 (0.016; 0.029)	0.021 (0.016; 0.029)	0.021 (0.016; 0.029)	0.021 (0.016; 0.029)
Placebo	0	0.005 (0.002; 0.016)	0.010 (0.006; 0.018)	0.015 (0.010; 0.023)	0.019 (0.014; 0.026)	0.029 (0.023; 0.035)	0.032 (0.027; 0.039)	0.035 (0.030; 0.042)	0.038 (0.032; 0.045)	0.039 (0.033; 0.045)	0.039 (0.033; 0.046)	0.039 (0.033; 0.046)	0.039 (0.033; 0.046)	0.039 (0.033; 0.046)	0.039 (0.033; 0.046)	0.039 (0.033; 0.046)

B. Randomized (naïve Day 01)



	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	141
Number at risk (censored)																
Vaccine	589 (0)	581 (1)	575 (1)	563 (6)	530 (32)	503 (56)	479 (78)	446 (106)	391 (158)	321 (228)	171 (377)	86 (462)	30 (518)	1 (547)	1 (547)	0 (548)
Placebo	588 (0)	579 (3)	569 (3)	558 (5)	531 (24)	501 (47)	468 (73)	432 (103)	387 (147)	323 (209)	164 (367)	87 (444)	29 (502)	1 (530)	1 (530)	0 (531)
Cumulative events																
Vaccine	0	7	13	20	27	31	32	37	40	40	41	41	41	41	41	41
Placebo	0	7	18	26	34	41	49	53	55	56	57	57	57	57	57	57
Estimate (95% CI)																
Vaccine	0	0.012 (0.001; 0.071)	0.022 (0.007; 0.071)	0.034 (0.016; 0.074)	0.046 (0.026; 0.082)	0.054 (0.033; 0.088)	0.056 (0.035; 0.090)	0.066 (0.044; 0.099)	0.073 (0.050; 0.105)	0.073 (0.050; 0.105)	0.077 (0.054; 0.109)	0.077 (0.054; 0.109)	0.077 (0.054; 0.109)	0.077 (0.054; 0.109)	0.077 (0.054; 0.109)	0.077 (0.054; 0.109)
Placebo	0	0.012 (0.001; 0.081)	0.031 (0.012; 0.081)	0.044 (0.023; 0.087)	0.058 (0.035; 0.097)	0.071 (0.047; 0.108)	0.087 (0.061; 0.122)	0.095 (0.069; 0.130)	0.099 (0.073; 0.134)	0.102 (0.075; 0.137)	0.105 (0.078; 0.140)	0.105 (0.078; 0.140)	0.105 (0.078; 0.140)	0.105 (0.078; 0.140)	0.105 (0.078; 0.140)	0.105 (0.078; 0.140)

C. Randomized (non-naïve Day 01)



	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	148
Number at risk (Censored)																
Vaccine	4864 (0)	4827 (16)	4825 (18)	4777 (65)	4376 (462)	3764 (1064)	3453 (1374)	3135 (1685)	2807 (2011)	1917 (2901)	601 (4217)	338 (4479)	123 (4694)	22 (4795)	18 (4799)	0 (4817)
Placebo	4838 (0)	4801 (16)	4783 (20)	4725 (59)	4315 (546)	3693 (1034)	3390 (1330)	3087 (1625)	2742 (1964)	1842 (2862)	593 (4111)	33 (4373)	118 (4586)	25 (4679)	17 (4687)	0 (4704)
Cumulative events																
Vaccine	0	21	21	22	27	36	38	45	46	46	46	47	47	47	47	47
Placebo	0	23	37	55	70	111	118	127	132	134	134	134	134	134	134	134
Estimate (95% CI)																
Vaccine	0	0.004 (0.001; 0.019)	0.004 (0.001; 0.019)	0.005 (0.001; 0.019)	0.006 (0.002; 0.019)	0.008 (0.003; 0.019)	0.008 (0.004; 0.019)	0.011 (0.005; 0.021)	0.011 (0.006; 0.021)	0.011 (0.006; 0.021)	0.011 (0.006; 0.021)	0.014 (0.008; 0.023)	0.014 (0.008; 0.023)	0.014 (0.008; 0.023)	0.014 (0.008; 0.023)	0.014 (0.008; 0.023)
Placebo	0	0.005 (0.001; 0.017)	0.008 (0.003; 0.017)	0.011 (0.007; 0.020)	0.015 (0.010; 0.022)	0.025 (0.019; 0.032)	0.027 (0.021; 0.034)	0.029 (0.024; 0.036)	0.031 (0.025; 0.038)	0.032 (0.026; 0.039)	0.032 (0.026; 0.039)	0.032 (0.026; 0.039)	0.032 (0.026; 0.039)	0.032 (0.026; 0.039)	0.032 (0.026; 0.039)	0.032 (0.026; 0.039)

2.10 Survival analyses based on the Stratified Cox proportional hazard model

Based on the Stratified Cox proportional hazard model, the VE for symptomatic COVID-19 was 64.3% (95% CI: 46.5; 76.2), the VE for severe COVID-19 wads -58.2 (95% CI -847.1; 73.6) and the VE for hospitalized COVID-19 was 100.0 (95% CI NC; 100.0).

2.11 Vaccine efficacy in the mFAS-PD1 subset

All cases correspond to one episode.

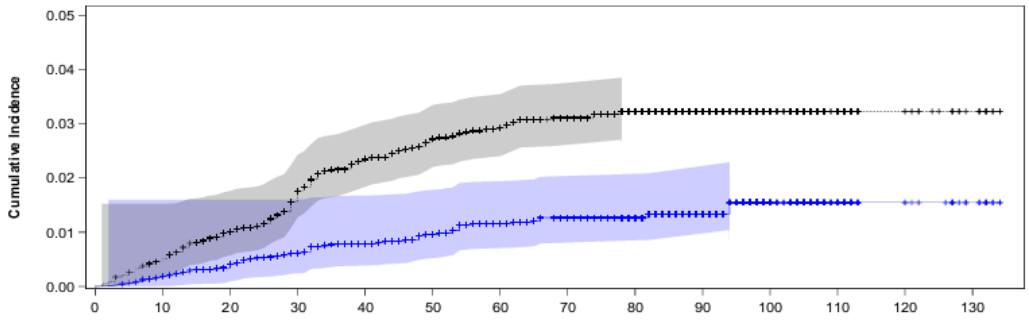
	Vaccine group (n=6,418)	**Placebo group (n=6,391)**	**Vaccine efficacy, % (95% CI)**
Symptomatic COVID-19			
Cases	68	169	..
1000 person-years at risk	1·069	1·055	..
Incidence rate (95% CI)	63·593 (49·38–80·62)	160·144 (136·91–186·19)	60·3 (47·1–70·5)
Participants at risk, n	6,418	6,390	..
Cumulative incidence, % (95% CI)	1·1 (0·8–1·3)	2·6 (2·3–3·1)	59·9 (46·6–70·2)
Severe COVID-19			
Cases	6	8	..
1000 person-years at risk	1·069	1·055	..
Incidence rate (95% CI)	5·611 (2·06–12·21)	7·581 (3·27–14·94)	26·0 (-143·3–78·8)
Participants at risk, n	6,418	6,390	..
Cumulative incidence, % (95% CI)	0·1 (0–0·2)	0·1 (0·1–0·2)	25·3 (-145·4–78·6)

Incidence rate: cases per 1000 person-years at risk
Subjects at risk: subjects with censor date after 14 days post-injection 1 in the analysis population
Cumulative incidence: cases divided by number of subjects at risk in each group * 100

CI, confidence interval.

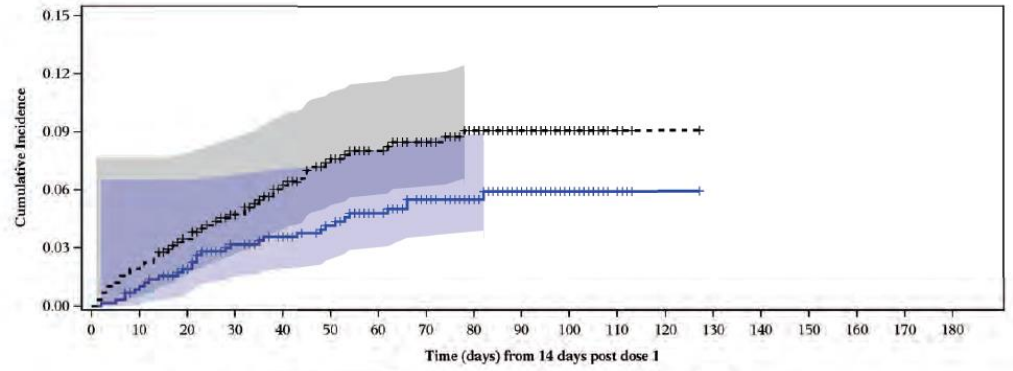
2.12 Kaplan-Meier cumulative incidence of symptomatic COVID-19 in the mFAS-PD1 population (overall, naïve and non-naïve populations)

A. Overall



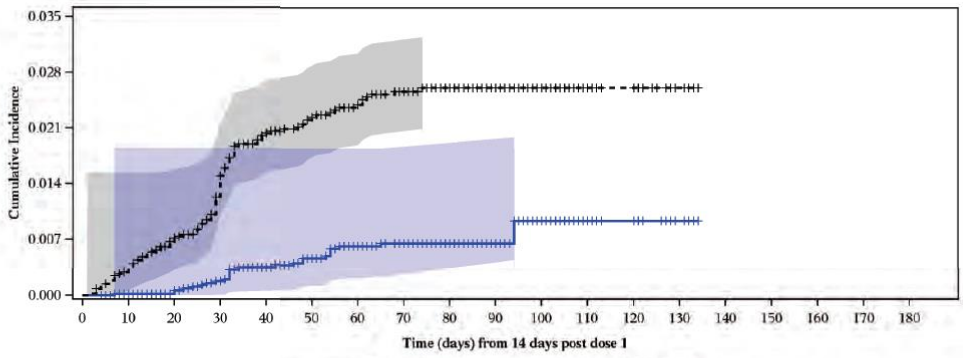
Number at Risk														
Vaccine Group	6418	6388	6106	5330	4458	4088	3735	3370	1618	750	263	82	23	11
Placebo Group	6390	6347	6052	5271	4383	4016	3661	3291	1576	738	255	86	26	12
Cumulative Events														
Vaccine Group	0	12	26	38	47	54	62	66	66	67	68	68	68	68
Placebo Group	0	33	64	106	135	151	159	166	169	169	169	169	169	169

B. Naïve at baseline



Number at Risk														
Vaccine Group	577	570	546	517	494	461	432	380	256	151	47	13	1	0
Placebo Group	576	565	545	523	486	451	415	377	261	142	44	15	1	0
Cumulative Events														
Vaccine Group	0	6	11	18	20	23	26	29	29	30	30	30	30	30
Placebo Group	0	12	20	27	35	42	44	46	48	48	48	48	48	48

C. Non-naïve at baseline



Number at Risk														
Vaccine Group	4826	4809	4604	4120	3571	3347	3037	2745	1190	513	205	69	22	11	0
Placebo Group	4792	4764	4544	4054	3492	3287	2985	2672	1136	512	203	71	25	12	0
Cumulative Events															
Vaccine Group	0	1	3	8	15	19	24	25	25	25	26	26	26	26	26
Placebo Group	0	16	34	67	88	95	100	105	106	106	106	106	106	106	106

2.13 Vaccine efficacy in the mFAS-PD2 population according to country, race/ethnic subgroups and risk of severe disease

		Vaccine group (n=5,736)	Placebo group (n=5,680)	Vaccine efficacy, % (95% CI)
Country	**Colombia**			
	Cases	3	7	..
	1000 person-years at risk	0·020	0·018	..
	Incidence rate (95% CI)	149·938 (30·92–438·18)	385·459 (154·97–795·19)	61·1 (-70·4–93·5)
	Participants at risk, n	328	319	..
	Cumulative incidence, % (95% CI)	0·9 (0·2–2·6)	2·2 (0·9–4·5)	58·3 (-82·6–93·0)
	Ghana			
	Cases	0	1	..
	1000 person-years at risk	0·007	0·068	..
	Incidence rate (95% CI)	0 (0–558·38)	14·635 (0·37–81·54)	100 (-3614·1–100·0)
	Participants at risk, n	570	548	..
	Cumulative incidence, % (95% CI)	0 (0–0·6)	0·2 (0–1·0)	100 (-3649·5–100·0)
	India			
	Cases	6	29	..
	1000 person-years at risk	0·199	0·196	..
	Incidence rate (95% CI)	30·188 (11·08–65·71)	148·129 (99·2–212·74)	79·6 (50·0–93·1)
	Participants at risk, n	1628	1618	..
	Cumulative incidence, % (95% CI)	0·4 (0·1–0·8)	1·8 (1·2–2·6)	79·4 (49·6–93·0)
	Kenya			
	Cases	3	7	..
	1000 person-years at risk	0·151	0·149	..
	Incidence rate (95% CI)	19·915 (4·11–58·20)	47·042 (18·91–96·93)	57·7 (-85·4–92·9)
	Participants at risk, n	1620	1614	
	Cumulative incidence, % (95% CI)	0·2 (0–0·5)	0·4 (0·2–0·9)	57·3 (-87·0–92·9)
	Mexico			
	Cases	18	31	..
	1000 person-years at risk	0·042	0·040	..
	Incidence rate (95% CI)	432·590 (256·38–683·68)	772·357 (524·78–1096·30)	44·0 (-3·3–70·5)
	Participants at risk, n	320	317	..
	Cumulative incidence, % (95% CI)	5·6 (3·4–8·7)	9·8 (6·7–13·6)	42·5 (-6·1–69·7)
	Nepal			
	Cases	2	14	..
	1000 person-years at risk	0·115	0·115	..
	Incidence rate (95% CI)	17·400 (2·11–62·86)	121·860 (66·62–204·46)	85·7 (37·8–98·4)
	Participants at risk, n	738	760	–
	Cumulative incidence, % (95% CI)	0·3 (0–1·0)	1·8 (1·0–3·1)	85·3 (35·9–98·4)
	Uganda			
	Cases	0	0	..
	1000 person-years at risk	0·007	0·007	..
	Incidence rate (95% CI)	0 (0–558·38)	0 (0–545·05)	Not computed
	Participants at risk, n	107	2376	..

	Cumulative incidence, % (95% CI)	0 (0–3·4)	1·8 (1·3–2·4)	Not computed
Race/ Ethnicity	**Asian**			
	Cases	8	42	..
	1000 person-years at risk	0·313	0·310	..
	Incidence rate (95% CI)	25·539 (11·03–50·32)	135·278 (97·50–182·86)	81·1 (59·3–92·3)
	Participants at risk, n	2363	2376	..
	Cumulative incidence, % (95% CI)	0·3 (0·1–0·7)	1·8 (1·3–2·4)	80·8 (58·7–92·2)
	Black African or African American			
	Cases	3	8	..
	1000 person-years at risk	0·228	0·223	..
	Incidence rate (95% CI)	13·134 (2·71–38·38)	35·862 (15·48–70·66)	63·4 (-52·6–93·7)
	Participants at risk, n	2295	2268	..
	Cumulative incidence, % (95% CI)	0·1 (0–0·4)	0·4 (0·2–0·7)	62·9 (-54·4–93·7)
At risk of severe COVID-19*	**Aged 18–59 years**			
	Cases	10	28	..
	1000 person-years at risk	0·164	0·156	..
	Incidence rate (95% CI)	60·829 (29·17–111·87)	179·727 (119·43–259·76)	66·2 (28·2–85·3)
	Participants at risk, n	1429	1431	..
	Cumulative incidence, % (95% CI)	0·7 (0·3–1·3)	2·0 (1·3–2·8)	64·2 (24·1–84·5)
	Aged ≥65 years			
	Cases	1	0	..
	1000 person-years at risk	0·009	0·009	..
	Incidence rate (95% CI)	110·883 (2·81–617·80)	0 (0–409·53)	Not computed
	Participants at risk, n	83	82	..
	Cumulative incidence, % (95% CI)	1·2 (0–6·5)	0 (0–4·4)	Not computed
BMI	**Aged 18–59 years and BMI ≥30**			
	Cases	5	9	..
	1000 person-years at risk	0.048	0.043	..
	Incidence rate (95% CI)	104·155 (33·82; 243·06)	211·236 (96·59; 400·99)	50·7 (-63·8; 87·0)
	Participants at risk, n	430	399	..
	Cumulative incidence, % (95% CI)	1·2 (0·4; 2·7)	2·3 (1·0; 4·2)	48.4 (-71.3; 86.4)
	Aged 18–59 years and BMI <30			
	Cases	24	78	..
	1000 person-years at risk	0·524	0·518	..
	Incidence rate (95% CI)	45·798 (29·34; 68·14)	150·437 (118·91; 187·75)	69·6 (51·4; 81·6)
	Participants at risk, n	4570	4581	..
	Cumulative incidence, % (95% CI)	0·5 (0·3; 0·8)	1·7 (1·3; 2·1)	69·2 (50·7; 81·3)
	Aged ≥60 years and BMI ≥30			

	Cases	0	0	··
	1000 person-years at risk	0·002	0·004	··
	Incidence rate (95% CI)	0 (0; 2101·97)	0 (0; 873·21)	Not computable
	Participants at risk, n	19	43	··
	Cumulative incidence, % (95% CI)	0 (0; 17·6)	0 (0; 8·2)	Not computable
	Aged ≥60 years and BMI <30			
	Cases	3	2	··
	1000 person-years at risk	0·031	0·028	··
	Incidence rate (95% CI)	98·326 (20·28; 287·35)	72·622 (8·79; 262·33)	-35·4 (-1521·1; 84·5)
	Participants at risk, n	292	264	··
	Cumulative incidence, % (95% CI)	1·0 (0·2; 3·0)	0·8 (0·1; 2·7)	-35·6 (-1523·7; 84·5)

*Comorbidities associated with increased risk of severe COVID-19 are listed above. All cases correspond to one episode. Incidence rate" is the "incidence expressed by 1000 patient-years at risk.

CI, confidence interval.

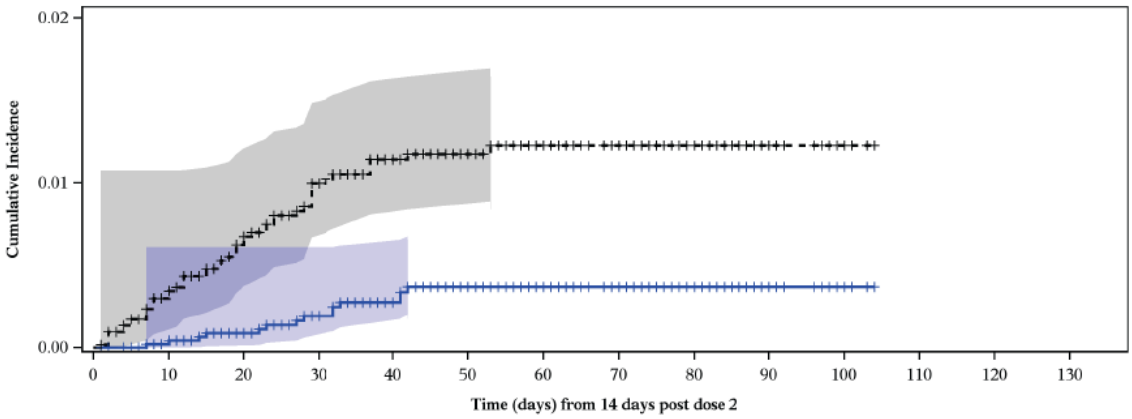
2.14 Vaccine efficacy against asymptomatic SARS-CoV-2 infection in naïve participants

Cases: number of subjects with ≥1 occurrence of relevant endpoint from 14 days post-injection (1 or 2 as applicable) in the analysis population.

	mFAS-PD1 Naïve-D1			**mFAS-PD2 Naïve-D1+D22**		
	Vaccine group (n=577)	Placebo group (n=576)	Vaccine efficacy, % (95% CI)	Vaccine group (n=315)	Placebo group (n=333)	Vaccine efficacy, % (95% CI)
Cases	275	266		100	107	
Cumulative incidence, % (95% CI)	47·7 (43·5–51·8)	46·2 (42·1–50·3)	–3·2 (-22·6–13·1)	31·7 (26·6–37·2)	32·1 (27·1–37·4)	1·2 (-31·0–25·5)

mFAS-PD1, modified full analysis set post dose 1; mFAS-PD2, modified full analysis set post dose 2.

2.15 Cumulative incidence of symptomatic Omicron infections in the mFAS-PD2 set



Number at Risk												
Vaccine Group	5311	4512	4142	3604	3295	2227	1017	559	220	30	16	0
Placebo Group	5287	4441	4071	3519	3232	2169	977	539	219	36	14	0
Cumulative Events												
Vaccine Group	0	2	4	8	11	14	14	14	14	14	14	14
Placebo Group	0	17	31	43	48	49	50	50	50	50	50	50

2.16 Sensitivity analysis: efficacy against Symptomatic COVID-19 caused by Omicron or undefined variants in the mFAS-PD2 population

	Vaccine group (n=5,736)			**Placebo group (n=5,680)**			
	Cases	1000 Person-years at risk	Incidence rate (95% CI)	Cases	1000 Person-years at risk	Incidence rate (95% CI)	Vaccine efficacy, % (95% CI)
All participants	32	0·604	52·953 (36·22; 74·75)`	85	0·593	143·373(114·52; 177·28)	63·1 (43·9; 76·2)
Naïve participants	15	0·048	312·233 (174·75; 514·98)	21	0·049	431·495 (267·10; 659·59)	27·6 (-47·3; 65·3)
Non-naïve participants	16	0·528	30·306 (17·32; 49·22)	60	0·518	115·722 (88·31; 148·96)	73·8 (53·9; 85·9)

Cases: number of participants with ≥1 symptomatic COVID-19 episode from 14 days post-injection 2 in the analysis population
Cumulative incidence: cases divided by the number of participants in each group * 100

CI, confidence interval.

2.17 Safety overview after injection 1 and injection 2 in all participants – RsafAS/SafAS

	Post injection 1						Post injection 2					
	Vaccine group (N=6472)			Placebo group (N=6450)			Vaccine group (N=5788)			Placebo group (N=5755)		
Participants experiencing at least one:	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
SafAS												
Within 30 minutes after injection												
Immediate unsolicited AE	4/6472	<0·1	(0; 0·2)	4/6450	<0·1	(0; 0·2)	0/5788	0	(0; 0·1)	3/5755	<0·1	(0; 0·2)
Immediate unsolicited AR	4/6472	<0·1	(0; 0·2)	3/6450	<0·1	(0; 0·1)	0/5788	0	(0; 0·1)	3/5755	<0·1	(0; 0·2)
RSafAS												
Solicited reaction within solicited period after injection												
Solicited reaction	1119/2420	46·2	(44·2; 48·3)	685/2403	28·5	(26·7; 30·4)	911/2271	40·1	(38·1; 42·2)	629/2259	27·8	(26·0; 29·7)
Grade 3 solicited reaction	124/2420	5·1	(4·3; 6·1)	82/2403	3·4	(2·7; 4·2)	110/2271	4·8	(4·0; 5·8)	57/2259	2·5	(1·9; 3·3)
Solicited injection site reaction	862/2419	35·6	(33·7; 37·6)	412/2403	17·1	(15·7; 18·7)	720/2270	31·7	(29·8; 33·7)	376/2258	16·7	(15·1; 18·3)
Grade 3 solicited injection site reaction	58/2419	2·4	(1·8; 3·1)	30/2403	1·2	(0·8; 1·8)	54/2270	2·4	(1·8; 3·1)	20/2258	0·9	(0·5; 1·4)
Solicited systemic reaction	818/2420	33·8	(31·9; 35·7)	560/2403	23·3	(21·6; 25·0)	690/2271	30·4	(28·5; 32·3)	520/2259	23·0	(21·3; 24·8)
Grade 3 solicited systemic reaction	104/2420	4·3	(3·5; 5·2)	75/2403	3·1	(2·5; 3·9)	91/2271	4·0	(3·2; 4·9)	52/2259	2·3	(1·7; 3·0)
Within 21 days after injection												
Unsolicited AE	97/2433	4·0	(3·2; 4·8)	113/2418	4·7	(3·9; 5·6)	78/2276	3·4	(2·7; 4·3)	99/2271	4·4	(3·6; 5·3)
Unsolicited AR	14/2433	0·6	(0·3; 1·0)	11/2418	0·5	(0·2; 0·8)	13/2276	0·6	(0·3; 1·0)	5/2271	0·2	(0·1; 0·5)
Unsolicited non-serious AE	90/2433	3·7	(3·0; 4·5)	108/2418	4·5	(3·7; 5·4)	75/2276	3·3	(2·6; 4·1)	96/2271	4·2	(3·4; 5·1)
Unsolicited non-serious AR	14/2433	0·6	(0·3; 1·0)	11/2418	0·5	(0·2; 0·8)	13/2276	0·6	(0·3; 1·0)	5/2271	0·2	(0·1; 0·5)
Unsolicited non-serious injection site AR	3/2433	0·1	(0; 0·4)	0/2418	0	(0; 0·2)	1/2276	<0·1	(0; 0·2)	0/2271	0	(0; 0·2)
Unsolicited non-serious systemic AE	87/2433	3·6	(2·9; 4·4)	108/2418	4·5	(3·7; 5·4)	74/2276	3·3	(2·6; 4·1)	96/2271	4·2	(3·4; 5·1)
Participants experiencing at least one:												
Unsolicited non-serious systemic	11/2433	0·5	(0·2; 0·8)	11/2418	0·5	(0·2; 0·8)	12/2276	0·5	(0·3; 0·9)	5/2271	0·2	(0·1; 0·5)

AR												
SafAS												
Within 21 days after injection												
AE leading to study discontinuation	2/6472	<0·1	(0; 0·1)	0/6450	0	(0; 0·1)	0/5788	0	(0; 0·1)	2/5755	<0·1	(0; 0·1)
SAE	11/6472	0·2	(0·1; 0·3)	8/6450	0·1	(0·1; 0·2)	6/5788	0·1	(0; 0·2)	6/5755	0·1	(0; 0·2)
Death	1/6472	<0·1	(0; 0·1)	0/6450	0	(0; 0·1)	0/5788	0	(0; 0·1)	2/5755	<0·1	(0; 0·1)
AESI (including pIMDs)	1/6472	<0·1	(0; 0·1)	1/6450	<0·1	(0; 0·1)	0/5788	0	(0; 0·1)	0/5755	0	(0; 0·1)
MAAE	169/6472	2·6	(2·2; 3·0)	172/6450	2·7	(2·3; 3·1)	101/5788	1·7	(1·4; 2·1)	112/5755	1·9	(1·6; 2·3)

Abbreviations: AE: adverse event; AESI: adverse event of special interest; AR: adverse reaction; MAAE: medically attended adverse event; pIMDs: potential immune-mediated diseases; RSafAS, reactogenicity safety analysis set; SAE: serious adverse event; SafAS, safety analysis set.

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint

2.18 Additional safety outcomes

- Observed SISRs and SSRs were mostly mild to moderate in severity, started within 3 days after the injection and spontaneously resolved within 1–3 days. The type, incidence and severity of SISRs and SSRs were comparable after both injections, irrespective of participant age.
- Ten (<0·1%) participants (five [<0·1%] in the Vaccine Group and five [<0·1%] in the Placebo Group), reported discontinuation from the study due to an AE; all AEs were assessed as not related to the study intervention.
- Up to the analysis cut-off date, 49 participants reported a pregnancy. Based on limited data (pregnancy precluded eligibility to the study), no safety concern was identified among pregnant women.
- There was no evidence of an increased risk of severe COVID-19 in the vaccine group compared with the placebo group. There were no fatal COVID-19 cases and a limited number of severe COVID-19 and hospitalized COVID-19 cases.

References

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