SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1 NAME OF THE MEDICINAL PRODUCT

GEMCOVAC®-OM.

GEMCOVAC®-OM is indicated as a booster for active immunization for the prevention of COVID-19 in individuals 18 years of age and older who have received either COVAXIN® or COVISHIELD™ as primary vaccination.

Lyophilized mRNA Vaccine for Injection (COVID-19) 10 µg/ Dose
[10 µg/ 0.1 mL] [Omicron variant - sublineage BA.1]
Presentation: 5 dose/ vial

2 QUANTITATIVE AND QUALITATIVE COMPOSITION

Active

S. No.	Name of Ingredient	Pharmacopoeial Monograph	Quantity/ Dose	Quantity/ Vial of 5 dose
1	mRNA (*in vitro* transcribed mRNA encoding for the Spike (S)- protein of the SARS-CoV-2 virus (Omicron variant)	In House	10 µg	50 µg

For the full list of excipients, see section 6.1.

S. No.	Name of Ingredient	Pharmacopoeial Monograph	Quantity/ Dose	Quantity/ Vial of 5 dose
1	DOTAP	In House	0.30 mg	1.50 mg
2	Squalene	BP/ Ph. Eur	0.38 mg	1.9 mg
3	Sorbitan Monostearate	BP/ Ph. Eur	0.37 mg	1.85 mg
4	Polysorbate 80	I.P./BP/Ph. Eur./USP	0.37 mg	1.85 mg
5	Sucrose	I.P./BP/Ph. Eur.	10.0 mg	50.0 mg
6	Citric Acid Monohydrate	I.P./BP/Ph. Eur./IH	1.05 mg	5.25 mg

3 PHARMACEUTICAL FORM

GEMCOVAC®-OM is a lyophilized powder that needs to be reconstituted with Sterile Water for Injection (SWFI) before administration. The reconstituted solution is an off-white liquid free from any visible particles. Each dose of 0.1 mL contains 10 µg of GEMCOVAC®-OM mRNA vaccine.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

GEMCOVAC®-OM is indicated as a booster for active immunization for the prevention of COVID-19 in individuals 18 years of age and older and have received either COVAXIN® or COVISHIELD™ as primary vaccination.

4.2 Posology and method of administration Posology

GEMCOVAC®-OM should be administered in single dose in individuals aged ≥ 18 years administered at least 4 months after completion of primary vaccination with either COVISHIELD™ or COVAXIN®. A volume of 0.1 mL should be administered intradermally using a Needle- free Tropis® Injection system (PharmaJet, Colorado, USA).

Interchangeability

There is no safety, immunogenicity or efficacy data to support interchangeability of GEMCOVAC®- OM with any other COVID-19 vaccines.

Special Populations

Elderly population: No dose adjustment is required for the elderly population.

Pediatric population: The safety and efficacy of GEMCOVAC®-OM has not been established in children and adolescents < 18 years of age.

4.3 Contraindications

Hypersensitivity to any constituents of GEMCOVAC®-OM.

Individuals below 18 years of age.

4.4 Special warnings and precautions for use

- GEMCOVAC®-OM should not be administered intravenously, intramuscularly or subcutaneously.
- Hypersensitivity and Anaphylaxis: There is a risk of hypersensitivity reactions due to the constituents of GEMCOVAC®-OM. Supervision and if needed the appropriate medical treatment should be provided to all the vaccine recipients after immunization.

- Concurrent Illness: As with other vaccines, administration of GEMCOVAC®-OM should be postponed in individuals suffering from an acute severe febrile illness.
- GEMCOVAC®-OM should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy.
- Immunocompromised Individuals: It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.
- Anxiety related reactions: Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the vaccination. It is important that precautions are in place to avoid injury from fainting.
- Interchangeability: There are no safety, immunogenicity or efficacy data to support interchangeability of GEMCOVAC®-OM with any other COVID-19 vaccines.
- Reconstitution: GEMCOVAC®-OM is available as a lyophilized powder which needs to be reconstituted with Sterile Water for Injection. Draw 0.7 ml of sterile water and reconstitute vial respectively. Gently swirl the vial intermittently for approximately 180 seconds till all the lyophilized contents are dissolved and no particles are visible. The solution should be off white liquid free from any visible particles. Administer 0.1 mL of the reconstituted vaccine intradermally within 6 hours of reconstitution to the recipient. If not administered immediately after reconstitution, keep reconstituted vaccine back at +2º C to +8º C. vaccine is multi-dose. It will be used for dosing up to 5 recipients who must be dosed on same day within 6 hours of reconstitution.

4.5 Interaction with other medicinal products and other forms of Interaction

The safety, immunogenicity and efficacy of co-administration of GEMCOVAC®-OM with other vaccines or medications have not been evaluated.

4.6 Pregnancy and lactation

Safety, efficacy and immunogenicity have not been established in pregnant women and nursing mothers. It is unknown if GEMCOVAC®-OM is excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effect of GEMCOVAC®-OM on the ability to drive or use machines have been performed.

4.8 Undesirable Effects

4.8.1 Safety data from Phase II Clinical Trial

The Phase II clinical trial was conducted in 140 participants. The safety and immunogenicity of GEMCOVAC®-OM was compared with the GEMCOVAC®-19 which has received Emergency Use Authorization from Indian Regulatory Authority. The participants were randomized to the two vaccine arms in a 1:1 ratio. Participants included in this study received either COVAXIN® or COVISHIELD™ as their primary vaccination (two doses) at least 4 months back.

Table 1. Phase II clinical trial demography

Demography	**GEMCOVAC®-OM (n = 70)**	**GEMCOVAC®-19 (n = 70)**
Age, Median (min., max.)	32 (20, 49)	30 (20, 45)
Male, %	87.1%	91.4%
Weight, Mean (SD)	64.8 (5.07)	63.7 (5.17)
BMI, Mean (SD)	23.2 (1.67)	23.0 (1.54)

The clinical trial is ongoing and safety data up to Day 90 has been analyzed.

Local Solicited Adverse Events: A total of 3 participants (4.3%) receiving GEMCOVAC®-OM experienced at least one solicited local adverse event (AE) compared to 5 participants (7.1%) in the GEMCOVAC®-19 arm.

COVAXIN® primed subjects (n = 28): Only 1 local solicited AE (7.1%) was reported in a subject who received GEMCOVAC®-19 as a booster dose. It was mild in intensity.

COVISHIELD™ primed subjects (n = 112): 7 participants [GEMCOVAC®-19: 4 (7.1%); GEMCOVAC®-OM: 3 (5.4%)] reported at least one local solicited AE. Out of these 7 AEs, 4 were of Grade 1 intensity (mild) in GEMCOVAC®-19 and 2 AEs of Grade 1 intensity in GEMCOVAC®-OM. Only 1 AE of Grade 2 intensity (moderate) was observed in GEMCOVAC®-OM arm.

Pain at the injection site was the most common local solicited adverse event noted in 3 (4.3%) and 5 (7.1%) subjects in GEMCOVAC®-OM and GEMCOVAC®-19 groups respectively. No Grade 3 or higher adverse event was observed in participants receiving GEMCOVAC®-OM.

Systemic Solicited Adverse Events: A total of 6 participants [GEMCOVAC®-19: 4 (5.7%); GEMCOVAC®-OM: 2 (2.9%)] reported at least one systemic solicited AE.

COVAXIN® *primed subjects* (n = 28): No systemic solicited adverse events were reported.

COVISHIELD™ *primed subjects* (n = 112): 2 participants (2.9%) receiving GEMCOVAC®-OM experienced at least one solicited systemic adverse event compared to 4 participants (5.7%) in the GEMCOVAC®-19 arm. One AE in 1 (1.8%) subject who received GEMCOVAC®-OM as a booster dose was moderate in nature and rest of the AEs were mild.

In the participants who received GEMCOVAC®-19, fatigue was observed in 1 (1.4%) and pyrexia was observed in 1 (1.4%) subject. In both GEMCOVAC®-OM and GEMCOVAC®-19 arms, myalgia and headache were observed in 1 (1.4%) subject each. No Grade 3 or higher adverse event was observed in participants receiving GEMCOVAC®-OM.

No Serious Adverse Events (SAEs) or Adverse Event Special Interest (AESI) or COVID-19 cases were reported up to 3 months after the booster dose in either GEMCOVAC®-OM or GEMCOVAC®-19 arm.

4.8.2 Safety data from Phase III Clinical Trial

The Phase III clinical trial was conducted in 3140 participants who were randomized to receive either GEMCOVAC®-OM or COVISHIELD™. In Arm I, GEMCOVAC®-OM was administered as a booster dose to participants whose primary vaccination was either COVAXIN® or COVISHIELD™. In Arm II, COVISHIELD™ was administered as a booster to participants whose primary vaccination was COVISHIELD™.

The clinical trial is ongoing and safety data up to Day 90 has been analyzed.

Local Solicited Adverse Events: A total of 353 (11.8%) participants receiving GEMCOVAC®-OM and 18 (13.5%) participants receiving COVISHIELD™ experienced at least one local solicited adverse event.

COVAXIN® *primed subjects* (n = 622): A total of 73 (11.7%) participants who received GEMCOVAC®-OM as booster dose experienced at least one local solicited AE. All of them were of mild and moderate in intensity.

COVISHIELD™ *primed subjects* (n = 2501): A total of 280 (11.8%) participants who received GEMCOVAC®-OM and 18 (13.5%) participants who received COVISHIELD™ experienced at least one local solicited AE. Most of the local AEs were either mild or moderate in intensity.

Table 2. Phase III clinical trial demography

Demography	**GEMCOVAC®-OM (n = 2990)**	**COVISHIELD™ (n = 133)**
Age, Median (min., max.)	32.0 (18.0, 81.0)	32.0 (19.0, 57.0)
Male, %	68.2%	79.7%
Weight, Mean (SD)	62.6 (10.10)	63.9 (10.63)
BMI, Mean (SD)	23.6 (3.43)	23.8 (3.52)
Co-morbid Conditions		
Anemia, n (%)	1 (0.03%)	0 (0%)
Hypothyroidism, n (%)	1 (0.03%)	1(0.75%)
Diabetes Mellitus, n (%)	1 (0.03%)	0 (0%)
Obesity, n (%)	1 (0.03%)	0 (0%)
Hypertension, n (%)	7 (0.23%)	0 (0%)

In the participants receiving GEMCOVAC®-OM, pain at the injection site was the most common local solicited reaction in 275 (9.2%), followed by redness in 86 (2.9%), pruritus in 61 (2.0%), swelling in 48 (1.6%), warmth in 3 (0.1%) and bruising in 1 (0.1%) participant. Most of the local solicited adverse events were of Grade 1 and 2 severities. Only one case of Grade 3 (injection site bruising) event was observed in participant receiving GEMCOVAC®- OM.

Systemic Solicited Adverse Events: A total of 353 (11.8%) participants receiving GEMCOVAC®-OM and 16 (12.0%) participants receiving COVISHIELD™ observed at least 1 systemic solicited adverse event.

COVAXIN® primed subjects (n = 622): A total of 69 (11.1%) participants who received GEMCOVAC®-OM as booster dose experienced at least one systemic solicited AE. All of them were of mild and moderate in intensity.

COVISHIELD™ primed subjects (n = 2501): A total of 300 (12%) participants [GEMCOVAC®-OM: 284 (12.0%); COVISHIELD™: 16 (12.0%)] experienced at least one systemic solicited AE. All of them are mild and moderate in intensity.

In participants receiving GEMCOVAC®-OM, the most common systemic solicited event was fever in 197 (6.6%) followed by headache in 133 (4.4%), myalgia in 64 (2.1%), fatigue in 49 (1.6%), chills in 20 (0.7%), arthralgia in 21 (0.7%), nausea in 5 (0.2%), malaise in 3 (0.1%), vomiting in 2 (0.1%) and influenza like illness in 2 (0.1%). All of the systemic solicited AEs were of Grade 1 and 2 severities. No Grade 3 or higher adverse events were

observed in participants receiving GEMCOVAC®-OM.

Unsolicited Adverse Events: A total of 28 (0.94%) participants receiving GEMCOVAC®-OM and 2 (1.5%) of participants receiving COVISHIELD™ observed at least one unsolicited adverse event.

COVAXIN® primed subjects (n = 622): 4 AEs of systemic unsolicited Adverse Events were reported in 4 (0.64%) subjects who received GEMCOVAC®-OM as booster dose. Three unsolicited AEs were of mild category and 1 unsolicited AE was of moderate category.

COVISHIELD™ primed subjects (n = 2501): 26 systemic unsolicited AEs [GEMCOVAC®-OM: 24 (1.01%); COVISHIELD™: 2 (1.5 %)] were reported. Most of them were mild and moderate in nature except 2 severe in GEMCOVAC®-OM arm.

Serious Adverse Events (SAE): Three SAEs was reported in GEMCOVAC®-OM Arm (Omphalitis with umbolith, Spontaneous Abortion and Pulmonary Koch) which were not related to study vaccine.

Adverse drug reactions observed during the clinical trials were ranked using the following conventions:
Very Common : ≥ 1/10
Common : ≥ 1/100 to < 1/10
Uncommon : ≥ 1/1000 to < 1/100
Rare : ≥ 1/10000 to < 1/1000

Table 3. Adverse Events Observed in Phase III trial with GEMCOVAC®-OM

MedDRA System Organ Class	**Frequency**	**Adverse Event**
General Disorders and Administration Site Conditions	Common	Pain/Tenderness, Redness/Erythema, Swelling/Induration, Fatigue, Pruritus, Pyrexia
	Uncommon	Warmth, Chills, Malaise
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Uncommon	Arthralgia
Nervous System Disorders	Common	Headache
Gastrointestinal Disorders	Uncommon	Nausea, Vomiting
Skin And Subcutaneous Tissue Disorders	Uncommon	Rash

No cases of myocarditis/pericarditis (Adverse Event of Special Interest) or COVID-19 were reported in Phase II and III clinical trial up to Day 90.

4.9 Overdose

There is no data on overdose of GEMCOVAC®-OM

5 PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic Properties

5.1.1 Pre-clinical data

Immunogenicity preclinical Data:

The immunogenicity of GEMCOVAC®-OM was assessed in mice and guinea pigs. GEMCOVAC®-OM was injected into 10 C57BL/6 mice intramuscularly at 4 µg on Day 1 and Day 29. Blood was drawn at baseline, Day 28 and Day 43. There was an increase in the anti-spike IgG antibodies at Day 14, Day 28 and Day 43. Neutralizing antibodies assessed by cPASS™ and PRNT assay also showed an increase at Day 28 and Day 43 compared to the baseline.

Similarly, the immunogenicity of GEMCOVAC®-OM was assessed in guinea pigs. GEMCOVAC®-OM was administered intra-muscularly (2 and 5 µg) and intra-dermally (1, 2 and 5 µg) into 6 guinea pigs each at Day 1 and Day 29. Blood was drawn at baseline, Day 14, Day 28, Day 43 and Day 56. Vaccine administered by intradermal and intramuscular route induced immunogenic response in Guinea pigs at day 14, day 28, day 43 and day 56. At day 14, intradermal administration of 1µg, 2µg and 5µg dose generated higher immunogenic response than intramuscular 2µg and 5µg dose. At day 28 and day 43, immune response generated by 1µg intradermal dose was comparable to intramuscular 2µg and 5µg dose. Additionally, immunogenicity generated by intradermal administration of 2µg and 5µg dose was equivalent to intramuscular administration of 2µg and 5 µg at day 43. Intradermal administration of GEMCOVAC®-OM shows better immune response at day 14 (after prime dose) and show equivalent immune response after boost, day 43. Therefore, intradermal route of administration can be used for generating IgG titers comparable to intramuscular route of administration. We observed a significantly elevated omicron-spike-specific B cell population as well as IFNγ expressing T cells in the vaccinated guinea pig lymph nodes.

5.1.2 Immunogenicity from Phase II Clinical Trial

In the Phase II study, the safety and immunogenicity of GEMCOVAC®-OM was compared to GEMCOVAC®-19. A total of 140 participants who were ≥ 18 years and received COVAXIN® or COVISHIELD™ as their primary vaccination were randomized in a 1:1 ratio.

Anti-Spike IgG Antibodies: In the overall population, at Day 29, a statistically significant increase was seen in participants receiving both GEMCOVAC®-OM and GEMCOVAC®-19. The increase was greater with GEMCOVAC®-OM compared to GEMCOVAC®-19.

The Least Square Geometric Mean Ratio (LSGMR; GEMCOVAC®-OM/GEMCOVAC®-19) was 3.40 (95% CI: 2.79; 4.13) and was statistically significant ($p < 0.0001$) using ANCOVA with baseline titers as covariates.

Similar findings were observed on performing subgroup analysis in participants who received COVAXIN® and COVISHIELD™ as their primary immunization (Table 4).

Table 4. Anti-spike IgG antibodies in Phase II study

Time point	Primary vaccination COVAXIN		Primary vaccination COVISHIELD		Overall	
	GEMCOVAC-OM (n=14)	GEMCOVAC-19 (n=14)	GEMCOVAC-OM (n=56)	GEMCOVAC-19 (n=56)	GEMCOVAC-OM (n=70)	GEMCOVAC-19 (n=70)
Baseline GMT (95% CI)	23227.30 (13801.11, 39091.62)	30137.08 (19780.52, 45916.06)	32046.95 (24722.41, 41541.55)	37213.34 (29787.09, 46491.04)	30048.94 (23910.65, 37763.03)	35676.25 (29401.69, 43289.84)
Day 29 GMT (95% CI)	229202.48 (197702.41, 265721.49)	59528.52 (36959.75, 95878.49)	248405.33 (230771.99, 267386.04)	80365.02 (63797.84, 101234.40)	244440.18 (229122.30, 260782.13)	75683.05 (61687.58, 92853.78)

Seroconversion: Seroconversion rates were assessed by ≥2- fold rise in antibody (Anti-Spike IgG) titers at Day 29 from baseline. More subjects (65 [92.9%]) in the GEMCOVAC®-OM group achieved ≥2-fold rise in antibody titers as compared to subjects (40 [57.1%]) in the GEMCOVAC®-19 group. At Day 29, GMFR (Post-booster/Pre-booster vaccination) was greater in GEMCOVAC®-OM (8.13) compared to GEMCOVAC®-19 (2.12). The seroresponse rate difference between GEMCOVAC®-OM and GEMCOVAC®-19 calculated using Miettinen-Nurminen method was 35.71 (95% CI: 22.35; 48.52) which was statistically significant ($p < 0.0001$).

cPASS™ Neutralization Assay (Omicron Variant BA.1): The cPASS™ SARS-CoV-2 Surrogate Neutralization Antibody assay (Genscript) measures the neutralizing antibodies in blood sera of the participants. Rise in neutralizing antibodies (mean %, 95% CI) against SARS-CoV-2 at Day 29 was higher in GEMCOVAC®-OM (Day 29: 93.9%, 79.5, 88.36 vs. Baseline: 73.4%, 67.26, 79.48) as compared to GEMCOVAC®-19 (Day 29: 84.0%, 92.65, 95.20 vs. Baseline: 76.9 %, 71.34, 82.43). The difference of mean % change from baseline between GEMCOVAC®-OM and GEMCOVAC®-19 was 10.9 (95% CI: 7.02, 14.87) and was statistically significant ($p < 0.0001$).

Similar rise in neutralizing antibodies were observed on performing subgroup analysis on participants receiving COVAXIN® and COVISHIELD™ as their primary vaccination (Table 5).

Table 5. Neutralization by cPASS™ assay in Phase II study

Time point	Primary vaccination COVAXIN		Primary vaccination COVISHIELD		Overall	
	GEMCOVAC-OM (n=14)	GEMCOVAC-19 (n=14)	GEMCOVAC-OM (n=56)	GEMCOVAC-19 (n=56)	GEMCOVAC-OM (n=70)	GEMCOVAC-19 (n=70)
Baseline, Mean % (95% CI)	74.9 (61.78, 87.99)	82.5 (74.51, 90.40)	73.0 (65.90, 80.09)	75.5 (68.81, 82.18)	73.4 (67.26, 79.48)	76.9 (71.34, 82.43)
Day 29, Mean % (95% CI)	93.9 (91.66, 96.07)	88.2 (81.24, 95.16)	93.9 (92.41, 95.47)	82.9 (77.66, 88.17)	93.9 (92.65, 95.20)	84.0 (79.58, 88.36)

Cellular Immune Response: T-cell responses against the spike protein were assessed by using flow-cytometry based intracellular cytokine–staining (ICS) assay, on peripheral blood mononuclear cells (PBMCs). At Day 29, total T cell counts were comparable among both treatment arms. GEMCOVAC®-OM showed relatively higher median of IL-2^+ $CD4^+$ T-Cells. Additionally, GEMCOVAC®-OM showed significantly higher spike-specific IFNγ^+CD8^+, TNFα^+CD8^+ as well as IL-2^+ $CD8^+$ T-cells compared to baseline. GEMCOVAC®-OM showed relatively better cross-reactive T-cell responses, specially $CD8^+$ T-cell responses as compared to GEMCOVAC®-19.

5.1.3 Immunogenicity from Phase III Clinical Trial

The Phase III study was a non-inferiority study that compared the safety and immunogenicity of GEMCOVAC®-OM (n = 3000) with COVISHIELD™ (n = 140). The immunogenicity cohort consisted of 271 participants from the GEMCOVCAC®-OM arm and 133 from the COVISHIELD™ arm.

$PRNT_{50}$ Assay: Comparison of live virus neutralization using $PRNT_{50}$ assay against the SARS-CoV-2 (omicron variant) at Day 29 was the primary endpoint of the Phase III study. GMT of neutralizing antibodies was higher in the GEMCOVAC®-OM group at Day 29 as compared to baseline. No increase in the GMT was observed at Day 29 compared to baseline in COVISHIELD™ group. LSGMR between GEMCOVAC®-OM and COVISHIELD™ calculated using ANCOVA was 1.58 (95% CI: 1.36; 1.84; $p < 0.0001$). Since the lower bound 95% CI of LSGMR is 1.36, GEMCOVAC®-OM is non-inferior (> 0.67 pre-defined margin) to COVISHIELD™. A post-hoc analysis showed that the lower bound 95% CI of LSGMR is above the WHO defined margin of superiority (> 1).

Sub-group analysis of participants who received COVAXIN® and COVISHIELD™ as their primary vaccination showed similar findings (Table 6).

Table 6. Neutralization by $PRNT_{50}$ assay against Omicron variant of SARS-CoV-2 in Phase III study

Time point	Primary vaccination COVAXIN	Primary vaccination COVISHIELD		Overall	
	GEMCOVAC-OM (n=78)	GEMCOVAC-OM (n=193)	COVISHIELD (n=133)	GEMCOVAC-OM (n=271)	COVISHIELD (n=133)
Baseline, GMT (95% CI)	511.02 (381.57, 684.39)	676.44 (561.39, 815.07)	775.38 (620.28, 969.26)	623.99 (533.38, 729.98)	775.38 (620.28, 969.26)
Day 29 GMT (95% CI)	1043.97 (869.73, 1253.11)	1123.47 (1003.89, 1257.29)	754.97 (631.55, 902.51)	1099.98 (1000.00, 1209.97)	754.97 (631.55, 902.51)

Seroconversion by $PRNT_{50}$: At Day 29, more subjects in the GEMCOVAC®-OM (39.5%) group achieved ≥2-fold rise in antibody titers as compared with subjects in the COVISHIELD™ (19.5%) group. The seroresponse rate difference between GEMCOVAC®-OM and COVISHIELD™ was 19.93 (95% CI: 10.57: 28.43) which was statistically significant ($p < 0.0001$). Since the lower bound 95% CI (10.57) of difference in seroconversion is > -10%, GEMCOVAC®-OM vaccine is non-inferior to COVISHIELD™.

Anti-Spike IgG Antibodies: Anti-spike IgG antibodies for GEMCOVAC®-OM was higher compared to COVISHIELD™ at Day 29 (Table 7). At Day 29, GMFR was greater in GEMCOVAC®-OM (7.25) compared to COVISHIELD™ (3.29). The LSGMR of IgG between GEMCOVAC®-OM and COVISHIELD™ was 2.15 (95% CI: 1.83; 2.52) and was statistically significant using ANCOVA with baseline titers as covariates ($p < 0.0001$). Since the lower bound of 95% CI of LSGMR is > 0.67, GEMCOVAC®-OM is non-inferior to COVISHIELD™.

Subgroup analysis on participants who received COVAXIN® and COVISHIELD™ showed similar findings (Table 7).

Table 7. Anti-spike IgG antibodies in the Phase III study

Time point	Primary vaccination COVAXIN®	Primary vaccination COVISHIELD™		Overall	
	GEMCOVAC-OM (N=78)	GEMCOVAC-OM (N=193)	COVISHIELD™ (N=133)	GEMCOVAC-OM (N=271)	COVISHIELD™ (N=133)
Baseline, GMT (95% CI)	28736.67 (22858.46, 36126.51)	41351.61 (36677.70, 46621.14)	39206.84 (34052.97, 45140.75)	37239.20 (33398.06, 41522.11)	39206.84 (34052.97, 45140.75)
Day 29, GMT (95% CI)	262673.63 (210500.59, 327777.88)	273022.44 (244074.15, 305404.13)	128916.02 (109548.25, 151707.95)	270002.72 (243972.39, 298810.33)	128916.02 (109548.25, 151707.95)

Seroconversion by Anti-Spike IgG Antibodies: More subjects in the GEMCOVAC®-OM group (252 [93.0%]) achieved ≥ 2-fold rise in IgG antibody titers as compared to subjects in the COVISHIELD™ group (102 [76.7%]) at Day 29. The difference in the seroresponse rate using the Meitinen-Nurminen method between GEMCOVAC®-OM and COVISHIELD™ was 16.30 (95% CI: 9.02, 24.64) and was statistically significant ($p < 0.0001$). Since the lower bound of 95% CI (9.02) is > 10%, GEMCOVAC®-OM vaccine is non-inferior to COVISHIELD™.

cPASS™ Neutralization Assay (Omicron Variant BA.1): Neutralizing antibodies (mean) were higher at Day 29 compared to baseline with both GEMCOVAC®-OM (Day 29: 94% vs Baseline: 68.1%, $p < 0.0001$) and COVISHIELD™ (Day 29: 94.3% vs 68.6%, $p < 0.0001$; Table 6). At Day 29, mean % change from baseline (standard error [SE]) in neutralizing antibodies was 25.7 (0.67) and 26.0 (0.96) in GEMCOVAC®-OM and COVISHIELD™, respectively. The difference of mean % change from baseline between GEMCOVAC®-OM and COVISHIELD™ was -0.2 (95% CI: -2.51; 2.09) and was not statistically significant.

Subgroup analysis on participants receiving COVAXIN® and COVISHIELD™ showed similar results (Table 8).

Table 8. Neutralization by cPASS™ in Phase III

Time point	Primary vaccination COVAXIN®	Primary vaccination COVISHIELD™		Overall	
	GEMCOVAC-OM (N=78)	GEMCOVAC-OM (N=193)	COVISHIELD™ (N=133)	GEMCOVAC-OM (N=271)	COVISHIELD™ (N=133)
Baseline, GMT (95% CI)	62.2 (56.18, 68.25)	70.5 (66.65, 74.29)	68.6 (64.13, 73.08)	68.1 (64.85, 71.33)	68.6 (64.13, 73.08)
Day 29, GMT (95% CI)	89.5 (85.89, 93.21)	95.8 (94.65, 96.90)	94.3 (92.16, 96.37)	94.0 (92.63, 95.33)	94.3 (92.16, 96.37)

Cellular Immune Responses: Both the vaccine arms showed numerically higher IFNγ^+CD4$^+$ T-cells at Day 29 from the respective baseline. At Day 29, GEMCOVAC®-OM group showed numerically higher IFNγ^+CD4$^+$ T-cells and significantly elevated IL-2$^+$CD4$^+$ T-cells as compared to the baseline. TNFα expressions in CD4$^+$ T-cells in the GEMCOVAC®-OM cohort at Day 29 showed statistically significant increase when compared to the COVISHIELD™ group. At Day 29, both the vaccinated arms showed significantly higher spike-specific IFNγ^+ CD8$^+$T-cells and marked increase in TNFα $^+$CD8$^+$ T-cells. GEMCOVAC®-OM immunized subjects also showed significantly elevated IL-2 expressions in CD8$^+$ T-cells as compared to the baseline and as well as to the COVISHIELD™ vaccinated group. Spike-specific Th2 cytokines (IL-4 and IL-13) expressions in the T-cells from both the vaccinated cohorts were significantly lower when compared to the baseline

B cell responses to BA.1 and BA.5 were also assessed. At Day 29, GEMCOVAC®-OM immunized subject showed significantly elevated BA.1 specific B-cells as compared to the baseline as well as COVISHIELD™ booster vaccinated groups. GEMCOVAC®-OM immunized cohort showed significantly higher BA.5 reactive B-cells as compared to the COVISHIELD™ immunized cohort.

5.2 Preclinical safety data

A GLP-compliant skin irritation study was conducted in New Zealand white rabbits. GEMCOVAC®-OM was injected intradermally in a single dose at two sites, while the adjuvant control item was similarly injected at one site. No deaths or clinical signs of systemic toxicity were observed in treated rabbits during the period of this study. Body weights of treated rabbits were not affected during the study period. No gross pathological changes were observed during necropsy in tissues / organs of any of the rabbits in this

study, when sacrificed on Day 8. Observations of the skin revealed that intradermal injections to rabbits using the PharmaJet Tropis® device resulted in a reversible and a very slight, barely perceptible redness (grade 1) at the injection sites, not amounting to any significant irritation. Moreover, this minimal skin reaction, was comparable between the test vaccine and the adjuvant and hence was attributed not to the 'antigenic' components of the test vaccine, but to the ingredients of the adjuvant. It was found to be reversible in nature. Microscopic examination of all sites of intradermal injections revealed an inflammation in dermis that was minimal in severity, multifocal in spread, and characterized by infiltration of inflammatory cells, predominantly comprising of macrophages, and less of neutrophils. These alterations were of reversible nature and were identified as the desired pharmacological effects of the ingredients of the adjuvant, and non-adverse in nature. GEMCOVAC®-OM was found to be well tolerated at the intradermal injection sites in rabbit skin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

DOTAP
Squalene
Sorbitan Monostearate
Polysorbate 80
Sucrose
Citric Acid Monohydrate

6.2 Incompatibilities

In the absence of incompatibility studies, the vaccine should not be mixed with any other medicinal products.

6.3 Shelf life

The expiry date of lyophilized vaccine is indicated on the label and outer pack. Once reconstituted, the solution can be considered stable up to 6 hours when stored at +2ºC to +8ºC without opening flip-off seal and rubber stopper. All reconstituted multi-dose vials of GEMCOVAC®-OM should be discarded at the end of immunization session or within six hours whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2ºC to +8ºC). Do not freeze or shake the reconstituted solution.

6.5 Nature and contents of container

GEMCOVAC®-OM is presented in USP type I glass vial with bromobutyl stopper and Flip-off aluminium seal.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORIZATION PREQUALIFICATION HOLDER

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8 MARKETING AUTHORIZATION NUMBER(S)

PD/Vacc-06

9 DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Under EUA Filing

10 DATE OF REVISION OF THE TEXT

08th May 2023