Neutralization by cPASS was also assessed in 3 groups stratified by age (18 - ⩽ 40, > 40 - ⩽ 60 and > 60 years). The neutralization was > 90% in all the groups at Day 43 indicating a high protection against SARS-CoV-2 with GEMCOVAC™-19.

Table 8. Neutralization by surrogate virus assay (cPASS) at Day 43 in participants receiving GEMCOVAC™-19 stratified by age

Time Point \ Age	18 - ≤ 40 years (n = 349)	> 40 - ≤ 60 years (n = 114)	> 60 years (n = 14)
Day 43 [% (SD)]	94.5 (6.38)	95.5 (3.44)	96.7 (0.51)

Pseudovirus Neutralization Assay: The neutralizing antibodies using pseudovirus assay were evaluated in 40 participants of the immunogenicity cohort. A statistically significant rise in the GMT was observed at Day 43 compared to the baselines. The GMT at Day 43 were comparable between the two groups.

Table 9. Neutralization using pseudovirus in Phase III study

Time Point	GEMCOVAC™-19 (n = 27)	COVISHIELD™ (n = 13)
Baseline at Day 1 [GMT (95% CI)]	14.7 (7.7 – 27.9)	10.9 (4.2 – 27.8)
Day 43 [GMT (95% CI)]	323.6 (160.3 – 653.0)	384.4 (142.8 – 1034.7)

Seroconversion: Seroconversion rate assessed by a ≥ 2-fold rise in anti-Spike IgG titer in seropositive subjects and ≥ 4-fold rise in anti-spike IgG titer in seronegative subjects at Day 43 was similar in both the groups (94.1 % in GEMCOVAC™-19 and 91.1% in COVISHIELD™). GEMCOVAC™-19 was found to be non-inferior to COVISHIELD™.

Cellular Response: Cellular response was assessed in 122 subjects of the immunogenicity cohort. Both COVISHIELD™ and GEMCOVAC™-19 cohorts elicited vigorous spike-specific T-cell responses. These responses were biased towards T helper 1 cell (Th1) cytokines (IFNγ and TNFα) expression. Th2 cytokines (IL-4 and IL-13) expressions were very minimal or undetectable in both the vaccinated cohorts. Additionally, COVISHIELD™ and GEMCOVAC™-19 cohorts showed spike-specific poly-functional T-Cell responses. Both the vaccines showed elevated spike-specific memory B-Cell populations as compared to their respective baseline.

5.3 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

6. NONCLINICAL PROPERTIES
6.1 Animal Toxicology or Pharmacology
A GLP- compliant repeat dose toxicity study was conducted in wistar rats. A dose of 25 µg / 0.5 ml was administered once in 2 weeks over a period of 4 weeks (days 1, 15 and 29) along with control. GEMCOVAC™-19 administered intramuscularly was well tolerated by the rats. Treatment with GEMCOVAC™-19 did not cause any remarkable or adverse effects on the absolute and relative (% of body weight) values of weights of liver, kidneys, adrenals, testes / uterus (with cervix), brain, lungs and heart of the rats in this study. The necropsy examination of all rats conducted at termination of the study did not reveal any incidence of treatment related systemic pathology. No mortality occurred during the duration of the study. GEMCOVAC™-19 was found to be safe, immunogenic and well tolerated at the sites of injections.

Immunogenicity studies were conducted with GEMCOVAC™-19 in mice, rats and hamsters. The vaccine elicited robust humoral (binding and neutralizing antibodies), immune responses to the Spike antigen in different animal models.

Animal Challenge Study: GEMCOVAC™-19 efficacy in the prevention of SARS-CoV-2 infection was evaluated in virus challenge study conducted in Syrian Golden Hamsters. The results indicated that intramuscular administration of GEMCOVAC™-19 elicited immune responses that mitigated SARS-CoV-2 virus replication and pathogenesis significantly. The reduced viral replication and presence of SARS-CoV-2 neutralizing antibodies coincided with the reduced clinical signs and lung tissue pathology in vaccinated animals compared with the infected-unvaccinated groups.

7. DESCRIPTION
GEMCOVAC™-19 (COVID-19 mRNA Vaccine) is a lyophilized powder that needs to be reconstituted with sterile water before injection. GEMCOVAC™-19 is supplied as a lyophilized powder in multiple dose vials of 5 and 20 doses. For the 5 dose vial, draw 3 ml of water and for the 20 dose vial, draw 11 ml of water and reconstitute the vial. Gently swirl the vial intermittently for approximately 120 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. Inject IM 0.5 mL of the reconstituted vaccine solution within 6 hours of reconstitution to the recipient. If not administered within 30 minutes after reconstitution, keep reconstituted vaccine back at +2ºC to +8ºC. Recipients who must be dosed on same day within 6 hours of reconstitution.

8. PHARMACEUTICAL PARTICULARS
One dose of vaccine (0.5 ml) contains: mRNA (10 µg), DOTAP (0.3 mg), Squalene (0.376 mg), Sorbitan Monostearate (0.372 mg), Polysorbate 80 (0.372 mg), Citric Acid Monohydrate (1.05 mg) and Sucrose (50 mg).

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

8.2 Shelf life
The expiry date of lyophilized vaccine is indicated on the label and outer pack. Once reconstituted, 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™-19 should be discarded at the end of immunization session or within six hours whichever comes first.

8.3 Packaging information
GEMCOVAC™-19 Lyophilized mRNA Vaccine for Injection (COVID-19) is supplied in USP type I glass vial with Bromo-butyl rubber stopper and Flip-off Aluminium seal.

8.4 Storage and handling instructions
Store in a refrigerator (+2ºC to +8ºC). Do not freeze or shake the reconstituted solution. The vials should be used within 6 hours once opened. The vaccine should not be used beyond the expiry date as mentioned in the label.

9. PATIENT COUNSELLING INFORMATION
GEMCOVAC™-19 is a mRNA-based vaccine which uses Spike (S)-protein of the SARS-CoV-2 virus as an antigen. The body is expected to develop an immune response post vaccination which will help in prevention of severe COVID-19 disease. The most common adverse events reported with GEMCOVAC™-19 include injection site pain, fever and headache.
Inform the vaccine recipient of the potential benefits and risks of vaccination with GEMCOVAC™-19 and the importance of completing the 2 dose vaccination series. Advice the recipients to report any adverse event to their healthcare provider and by writing to **Safety@gennova.co.in**

10. DETAILS OF MANUFACTURER
GEMCOVAC™-19 is manufactured and Marketed by:
Gennova Biopharmaceuticals Limited
Block 1, Plot No. P-1 & P-2, I.T.B.T. Park,
Phase II, MIDC, Hinjawadi, Pune - 411 057, India.
TM Trade Mark Owned by
Gennova Biopharmaceuticals Ltd.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
MF/BIO/22/000064 dated 28-JUN-2022 under PD/Vacc-6

12. DATE OF REVISION
02nd July 2022

510020533IN02

For the Use Only of a Registered Medical Practitioner or a Hospital or a Laboratory

RESTRICTED USE IN EMERGENCY SITUATION OF COVID-19

Lyophilized mRNA Vaccine for Injection (COVID-19) 50 µg/5 Dose and 200 µg/20 Dose Vial

GEMCOVAC™-19

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1. GENERIC NAME
GEMCOVAC™-19, lyophilized powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One dose of 0.5 ml contains:

mRNA (In-*vitro* transcribed self amplifying mRNA encoding for the S-protein of SARS-CoV-2)	10.00 µg
DOTAP	0.30 mg
Squalene	0.376 mg
Sorbitan Monostearate	0.372 mg
Polysorbate 80	0.372 mg
Citric Acid Monohydrate	1.05 mg
Sucrose	50.00 mg

3. DOSAGE FORM AND STRENGTH
GEMCOVAC™-19 is a lyophilized powder that needs to be reconstituted with Sterile Water for Injections I.P. before administration. The reconstituted solution is off white liquid free from any visible particles. Each dose of 0.5 mL contains 10 µg of GEMCOVAC™-19 mRNA vaccine.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
GEMCOVAC™-19 is indicated for active immunization of individuals ≥18 years old for the prevention of COVID-19.

4.2 Posology and method of administration
Posology
GEMCOVAC™-19 should be administered in two doses, second dose after 28 days of the first dose. A volume of 0.5 ml should be administered intramuscularly. It is recommended that individuals who receive a first dose complete the vaccination course with GEMCOVAC™-19.

Method of administration
GEMCOVAC™-19 should be administered intramuscularly preferably in the deltoid muscle.

4.3 Contraindications
Hypersensitivity to any constituents of GEMCOVAC™-19
Individuals below 18 years of age

4.4 Special warnings and precautions for use
- GEMCOVAC™-19 should not be administered intravenously, intradermally or subcutaneously.
- Hypersensitivity and Anaphylaxis: There is a risk of hypersensitivity reactions due to the constituents of GEMCOVAC™-19. 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™-19 should be postponed in individuals suffering from an acute severe febrile illness.
- Risk of bleeding with intramuscular administration: As with other intramuscular injections, GEMCOVAC™-19 should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.
- 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 needle injection. 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™-19 with other COVID-19 vaccines.
- Reconstitution:
  5 Dose: GEMCOVAC™-19 is available as a lyophilized powder which needs to be reconstituted with Sterile Water for Injections I.P. Draw 3 ml of water and reconstitute the vial. Gently swirl the vial intermittently for approximately 120 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. Inject IM 0.5 mL of the reconstituted vaccine solution within 6 hours of reconstitution to the recipient. If not administered within 30 minutes after reconstitution, keep reconstituted vaccine back at +2ºC to +8ºC. This 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.
  20 Dose: GEMCOVAC™-19 is available as a lyophilized powder which needs to be reconstituted with Sterile Water for Injections I.P. Draw 11 ml of water and reconstitute the vial. Gently swirl the vial intermittently for approximately 120 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. Inject IM 0.5 mL of the reconstituted vaccine solution within 6 hours of reconstitution to the recipient. If not administered within 30 minutes after reconstitution, keep reconstituted vaccine back at +2ºC to +8ºC. This vaccine is multi-dose. It will be used for dosing up to 20 recipients who must be dosed on same day within 6 hours of reconstitution.

4.5 Drug interactions
The safety, immunogenicity and efficacy of co-administration of GEMCOVAC™-19 with other vaccines or medications have not been evaluated.

4.6 Use in special populations
Safety, efficacy and immunogenicity have not been established in pregnant women and nursing mothers. It is unknown if GEMCOVAC™-19 is excreted in human milk.
Paediatric population: The safety and efficacy of GEMCOVAC™-19 has not been established in children and adolescents < 18 years of age.
Elderly population: No dose adjustment is required for the elderly.

4.7 Effects on ability to drive and use machines
No studies on the effect of GEMCOVAC™-19 on the ability to drive or use machines have been performed.

4.8 Undesirable effects
Safety data from Phase I Clinical Trial
The Phase I clinical trial was conducted in 82 healthy subjects between the age of 18 and 70 years. Three dose strengths of 5 µg, 10 µg and 25 µg were compared with placebo. The primary endpoint of this study was to assess the safety, reactogenicity and tolerability of GEMCOVAC™-19 at the three dose strengths following 2 doses administered 28 days apart.
Local Solicited Adverse Event: There was no significant difference among the three dose strengths. The most frequent local adverse event was injection site pain, followed by induration/swelling and erythema/redness. Most of the solicited local AEs were of Grade 1 intensity. No immediate solicited AEs or solicited AEs of Grade 3 and above intensity were reported.
Systemic Solicited Adverse Event: The occurrence of systemic solicited adverse events was comparable between all dose strengths. Fatigue was most commonly reported, followed by headache and fever. Myalgia and chills were reported in less than 30% of the participants. Most of the solicited systemic AEs were of Grade 1 intensity. None of the adverse events were of Grade 3 and above as per the DAIDs criteria.
Unsolicited Adverse Events: All unsolicited adverse events except 5 were considered not related. The related adverse events were laboratory

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abnormalities which resolved completely. Most of the unsolicited AEs were of Grade 1 severity. No Grade 3 or higher adverse event was observed in participants receiving GEMCOVAC™-19. None of the adverse events led to death.

Serious Adverse Events: No related serious adverse events were observed in this study.

Safety data from Phase II Clinical Trial

The Phase II clinical trial was conducted in 415 participants. The safety and immunogenicity of GEMCOVAC™-19 was compared with the approved vaccine COVISHIELD™. The participants were randomized to the two arms in a 1:1 ratio.

Table 1. Phase II clinical trial demography

Demography	GEMCOVAC™-19 (n = 207)	COVISHIELD™ (n = 208)
Age [Median (min., max.)]	33.0 (18, 74)	34.0 (18, 69)
Male/Female [n]	137/70	138/70
Weight [Mean (SD)]	62.6 (12.82)	60.9 (10.22)
BMI [Mean (SD)]	23.75 (4.37)	23.29 (3.99)
Co-morbid Conditions		
Anaemia [n (%)]	3 (1.4)	4 (1.9)
Hypothyroidism [n (%)]	0	1 (0.5)
Diabetes Mellitus [n (%)]	3 (1.4)	3 (1.4)
Asthma [n (%)]	0	1 (0.5)
Hypertension [n (%)]	0	1 (0.5)

Local Solicited Adverse Events: A total of 107 participants (51.7%) receiving GEMCOVAC™-19 experienced at least one solicited local adverse event compared to 79 participants (38.0%) in the COVISHIELD™ arm. Although the local solicited events were higher in the GEMCOVAC™-19 arm, this difference was restricted to Grade 1 and 2 intensities. The Grade 3 and above adverse events were comparable between the two vaccine arms. In participants receiving GEMCOVAC™-19, pain at injection site was the most commonly observed event (47.3% of participants), followed by warmth (16.4% of participants), swelling/induration (9.2% of participants), erythema (2.4% of participants), pruritus (1.9% of participants) and bruising (0.5% of participants).

Systemic Solicited Adverse Events: A total of 100 participants (48.3%) receiving GEMCOVAC™-19 experienced at least one solicited systemic adverse event compared to 93 participants (44.7%) in the COVISHIELD™ arm at any dose. In the participants who received GEMCOVAC™-19, headache was most commonly observed (28.0% of participants), followed by fatigue (27.1% of participants), fever (23.7% of participants), myalgia (22.2% of participants), chills (17.4 % of participants), malaise (12.6% of participants), arthralgia (12.1% of participants) and nausea (6.3% of participants). Most of the solicited systemic adverse events were of Grade 1 intensity. Four subjects (1.9%) in the GEMCOVAC™-19 arm and 3 (1.4%) in the COVISHIELD™ arm reported solicited adverse events of Grade 3. One subject (0.5%) in the GEMCOVAC™-19 arm and 2 (1.0%) in the COVISHIELD™ arm reported solicited adverse event of Fever of Grade 4 intensity.

Unsolicited Adverse Events: A total of 20 participants (9.7%) in the GEMCOVAC™-19 arm and 25 participants (12.0%) in the COVISHIELD™ arm observed at least 1 unsolicited event following any vaccination. Of these adverse events, 5 in the GEMCOVAC™-19 arm were termed vaccine related (2 incidences of chest pain, 1 incidence of injection site pain, 1 incidence of dizziness and 1 incidence of urticaria).

Serious Adverse Events: A total of 8 serious adverse events were reported out of which 1 was fatal and related to COVISHIELD™ (Pulmonary Embolism). Other adverse events were termed not related to vaccine.

Safety data from Phase III Clinical Trial

The Phase III clinical trial was conducted in 4000 participants who were randomized to receive either GEMCOVAC™-19 or COVISHIELD™ in a 3:1 ratio.

Table 2. Phase III clinical trial demography

Demography	GEMCOVAC™-19 (n = 2992)	COVISHIELD™ (n = 998)
Age [Median (min., max.)]	33.0 (18, 81)	33.0 (18, 79)
Male/Female [n]	2348/644	781/217
Weight [Mean (SD)]	61.2 (11.30)	61.3 (11.20)
BMI [Mean (SD)]	22.46 (3.78)	22.53 (3.90)
Co-morbid Conditions		
Hypertension	13 (0.4)	2 (0.2)
History of hysterectomy [n (%)]	9 (0.3)	1 (0.1)
Hypothyroidism [n (%)]	4 (0.1)	0
Diabetes Mellitus [n (%)]	10 (0.3)	0
Uterine leiomyoma [n (%)]	1 (0)	0
Asthma [n (%)]	1 (0)	0

Local Solicited Adverse Events: A total of 928 (31.0%) of the participants receiving GEMCOVAC™-19 and 263 (26.4%) of the participants receiving COVISHIELD™ experienced at least one local solicited adverse event. In the participants receiving GEMCOVAC™-19, pain at the injection site was the most common local solicited reaction (27.5% of participants), followed by swelling at injection site (3.6% of participants), warmth at injection site (3.1% of the participants), redness at injection site (1.7% of participants), pruritus (0.4% of the participants) and bruising (0.1% of participants). None of the adverse events were above Grade 2.

Systemic Solicited Adverse Events: A total of 955 (31.9%) participants receiving GEMCOVAC™-19 and 340 (34.1%) participants receiving COVISHIELD™ observed at least 1 systemic solicited adverse event. In participants receiving GEMCOVAC™-19, the most common systemic solicited event was fever (15.6% of participants) followed by headache (12.9% of participants), fatigue (7.2% of participants), myalgia (6.9% of participants), chills (4.9% of participants), malaise (1.7% of participants), arthralgia (1.3% of participants) and nausea (1.3% of participants). Vomiting and influenza like illness was seen in < 1% of participants.

Unsolicited Adverse Events: A total of 51 (1.7%) participants receiving GEMCOVAC™-19 and 15 (1.5%) of participants receiving COVISHIELD™ observed at least one solicited adverse event. In the GEMCOVAC™-19 arm, of the 4 events were considered related to the vaccine (chest pain, uterine haemorrhage, angioedema and pruritus).

Serious Adverse Events: A total of 10 serious adverse events (7 in GEMCOVAC™-19 and 3 in COVISHIELD™) were observed. One serious adverse event of fever in COVISHIELD™ arm was related to the vaccine. The causality assessment of 1 serious adverse event in GEMCOVAC™-19 arm (Abnormal Uterine Bleeding) was considered as 'possibly related'.

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 Clinical trial with GEMCOVAC™-19

MedDRA System Organ Class	Frequency	Adverse Event
General Disorders and Administration Site Conditions	Very Common	Pain/Tenderness, Fever
	Common	Redness/Erythema, Swelling/Induration, Warmth, Chills, Malaise, Fatigue
	Uncommon	Pruritus, Bruising
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia
Nervous System Disorders	Very Common	Headache
Gastrointestinal Disorders	Common	Nausea
	Uncommon	Vomiting
Respiratory, thoracic and mediastinal disorders	Uncommon	Influenza like illness

No cases of myocarditis/pericarditis (Adverse Event of Special Interest) were reported in Phase I, II and III clinical trial.

4.9 Overdose

There is no data on overdose of GEMCOVAC™-19.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

GEMCOVAC™-19 uses the Spike (S) - protein of the SARS-CoV-2 virus as antigen which is reported to interact with host cells receptors (ACE-2). It uses a self-amplifying mRNA platform for slow and sustained release of S-protein for longer duration along with CLNE system for targeted vaccine delivery. Once administered intramuscularly, the *in vitro* transcribed mRNA encoding the S-protein is translated in the cytosol of the cells utilizing the cellular translational machinery. The S-protein synthesized represents the antigen, which then elicits the potent humoral and cellular immune responses.

5.2 Pharmacodynamic properties

Immunogenicity from Phase I Clinical Trial

A dose-ranging (5 µg, 10 µg and 25 µg), placebo-controlled, Phase I study was conducted in 82 health individuals between 18-70 years of age.

Anti-Spike IgG antibodies: There was a statistically significant rise in the anti-S- IgG GMT at Day 57 compared to baseline (Day 1) in the 5 µg, 10 µg and 25 µg. The GMT at Day 57 were 6408 (95% CI: 2330 – 17624) for the 5 µg group, 17013 (95% CI: 7115 – 40682) for the 10 µg group, 16266 (95% CI: 5777 – 45801) for the 25 µg group and 781 (95% CI: 397– 1535) in the placebo group.

cPASS Neutralization Assay: The cPass SARS-CoV-2 Surrogate Neutralization Antibody assay (Genscript) measures the neutralizing antibodies in blood sera of the participants. Sera collected from participants at Day 57 showed a high neutralization capacity of 97%, 96% and 93% for the 5 µg, 10 µg and 25 µg groups respectively.

Immunogenicity from Phase II Clinical Trial

In Phase II, the immunogenicity of GEMCOVAC™-19 was compared with that of COVISHIELD™ at Day 43.

Anti-Spike IgG Antibody: At Day 43, the IgG GMT was 216320 (95% CI:178561 - 262063) in the COVISHIELD™ arm and 282464 (95% CI:233994 - 340974) in the GEMCOVAC™-19 arm. The Least Square Geometric Mean Ratio (GEMCOVAC™-19: COVISHIELD™) was 1.267 and there was no statistically significant difference between the two.

$PRNT_{50}$ Assay: Plaque reduction neutralization test (PRNT) analysis was performed in a subset of the population in the two groups. At Day 43, the $PRNT_{50}$ GMT were 1085 (95% CI: 718 – 1639) in the COVISHIELD™ arm and 802 (95% CI: 420 – 1532) in the GEMCOVAC™-19 arm. There was no statistically significant difference in the $PRNT_{50}$ GMT at day 43 between the two groups.

cPASS Neutralization Assay: At Day 43, the neutralization capacity was at 93.3% (standard deviation: 9.99) in the COVISHIELD™ arm and 86.9% (standard deviation: 24.61) in the GEMCOVAC™-19 arm. There was no statistically significant difference between the two groups at Day 43.

Seroconversion: Seroconversion rate assessed by a ≥ 2-fold rise in anti-Spike IgG titer in seropositive subjects and ≥ 4-fold rise in anti-spike IgG titer in seronegative subjects at Day 43 was similar in both the groups (91.2% in GEMCOVAC™-19 and 93.7% in COVISHIELD™).

Cellular Immune Responses: 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). Both COVISHIELD™ and GEMCOVAC™-19 cohorts showed spike peptides stimulated IFNγ expression in CD4+ T-Cell at day-29. COVISHIELD™ cohort showed relatively higher IFNγ expressions in CD4+ T-cells, whereas GEMCOVAC™-19 generated relatively higher spike stimulated IL-2 expressions in CD4+ T-Cells. Both COVISHIELD™ as well as GEMCOVAC™-19 showed similar TNFα expressions in both CD4+ and CD8+ T-cells. Th2 cytokines (IL-4 and IL-13) expressions were very minimal or undetectable in both the vaccinated cohorts.

Immunogenicity from Phase III Clinical Trial

In Phase III non-inferiority study, the immunogenicity of GEMCOVAC™-19 was compared to COVISHIELD™ at Day 43 in 714 subjects.

GEMCOVAC™-19 was compared to COVISHIELD™ at Day 43 in 714 subjects.

Anti-Spike IgG Antibodies: Anti-Spike IgG antibodies were compared in a total of 714 participants of which 237 received COVISHIELD™ and 477 received GEMCOVAC™-19. There was a statistically significant rise in antibodies in both groups from baseline to Day 43. The GMT of GEMCOVAC™-19 was found to be non-inferior to COVISHIELD™.

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

Time Point	GEMCOVAC™-19 (n = 477)	COVISHIELD™ (n = 237)
Baseline at Day 1 [GMT(95% CI)]	11647.8 (9956.4 - 13626.6)	10200.0 (8018.9 - 12974.4)
Day 43 [GMT(95% CI)]	339930.2 (311391.4 - 371084.5)	319605.1 (281630.1 - 362700.6)

The anti-Spike IgG antibodies were also analyzed in 3 groups stratified by age (18 - ≤ 40, > 40 - ⩽ 60 and > 60 years). There was no reduction in the Anti-Spike IgG titer at Day 43 with GEMCOVAC™-19 and no dose adjustment is required for older age groups more than 60 years of age.

Table 5. Anti-Spike IgG Antibodies at Day 43 in participants receiving GEMCOVAC™-19 stratified by age

Time Point \ Age	18 - ≤ 40 years (n = 349)	> 40 - ≤ 60 years (n = 114)	> 60 years (n = 14)
Day 43 [GMT(95% CI)]	322099.8 (290152.0 - 357565.2)	369352.3 (311528.3 - 437909.4)	662433.1 (441229.4 - 994533.8)

$PRNT_{50}$ Assay: $PRNT_{50}$ analysis was performed using the D614G variant of SARS-CoV-2 in 76 participants. There was a substantial increase in the neutralizing antibodies in both the arms from baseline till Day 43. Neutralizing antibody GMT in GEMCOVAC™-19 arm was found to be comparable to COVISHIELD™ arm.

Table 6. Neutralization by $PRNT_{50}$ assay against D614G variant of SARS-CoV-2 in Phase III study

Time Point	GEMCOVAC™-19 (n = 51)	COVISHIELD™ (n = 25)
Baseline at Day 1 [GMT(95%CI)]	29.3 (16.7 - 51.6)	31.1 (13.6 - 70.9)
Day 43 [GMT(95%CI)]	1099.9 (817.9 – 1479.2)	841.6 (461.5 – 1534.8)

cPASS Neutralization Assay: cPASS assay was performed in all 714 participants of the immunogenicity cohort. There was a statistically significant rise in the neutralizing antibodies in both the groups from baseline to Day 43. The percent neutralization was comparable in both groups at Day 43.

Table 7. Neutralization by cPASS assay in Phase III study

Time Point	GEMCOVAC™-19 (n = 477)	COVISHIELD™ (n = 237)
Baseline at Day 1 [% (SD)]	44.8 (33.75)	44.5 (34.40)
Day 43 [% (SD)]	94.8 (5.74)	93.9 (7.59)