CT Application(s) Summary Report

- **Protocol title:** A Phase III, Randomized, Double Blind, Placebo-Controlled International Multisite Clinical Trial in Parallel Assignment to Evaluate Efficacy, Immunogenicity and Safety of the Sputnik Light Vector Vaccine in Adults in the SARS-CoV-2 Infection Prophylactic Treatment.
- **Protocol code number**: 01-Sputnik-Light-2021
- ***Public Registry Number***: NCT04741061
- **Version:** 3.1
- **Date:** 17/06/2021

- **Investigational Medicinal Product being tested:**

Biological	■	**Pharmaceutical**	☐	**Innovative**	☐
Herbal medicine	☐	**Medical device**	☐		

- **Sponsor:**

-The Global Sponsor: Human Vaccine LLC

-Vaccine Development Company and Local Sponsor in Russia: Russian Ministry of Healthcare FGBU N.F. Gamaleya Scientific Research Center of Epidemiology and Microbiology

- **Indication:** Helping prevent the new coronavirus infection (COVID-19) in above 18 years old.

- **Investigator's brochure (IB)**

Version: 1.0
Date: 30/12/2020

- **Name of all Sites:**
  -Katameya medical center.
  -National Hepatology and Tropical Medicine Center
- **Name of PI(s):** Dr: Mohamed Hassany Barbary

- **EDA approval date:**

1.Initial approval for protocol version 3.1 and IB Version 1.0 on: 24/08/2021

2. Amendment of ICF V3.0 for Participant Information Sheet and Informed Consent Form and ICF V3.0 for Participant Information Sheet and Informed Consent Form for Participation in the additional Immunogenicity Study approval date: 27/09/2021

- **Summary of pre-clinical studies:**

A. Nonclinical Pharmacology

The results of the nonclinical pharmacology data for the recombinant adenoviral vector vaccine (Sputnik Light) expressing the SARS-CoV-2 spike (S)glycoprotein focused on primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology.

- **Primary Pharmacodynamics:**

Mechanism of Action: The vaccine is based on a replication-defective recombinant human adenovirus serotype 26 (Ad26) vector encoding the SARS-CoV-2 spike (S) protein. Following intramuscular administration, the vector enters host cells via CAR and integrin receptors, resulting in intracellular delivery of episomal DNA and transient expression of the S antigen. This leads to induction of antigen-specific humoral and cellular immune responses.

In vivo studies using luciferase reporter constructs demonstrated that transgene expression is localized to the injection site (muscle tissue).

Peak expression was observed at Day 2 post-administration, with no detectable expression by Day

Immunogenicity: The studies were conducted in mice (BALB/c, females, 18–20 g). Animals received intramuscular injections (200 µL), and serum samples were collected at Day 14 post-immunization.

The vaccine induced robust IgG antibody responses against the SARS-CoV-2 S glycoprotein, with mean titers meeting or exceeding the predefined specification threshold of ≥1:250.

Conclusion: The primary pharmacodynamic data demonstrate that the vaccine induces localized antigen expression and elicits a robust humoral immune response consistent with its intended prophylactic mechanism.

- **Secondary Pharmacodynamics:**

Quantitative PCR analysis following a single intramuscular administration demonstrated that the highest levels of adenoviral vector DNA were detected at the injection site (muscle) at 6 hours post-dose. Limited distribution was observed in lymphoid and systemic tissues (lymph nodes, spleen, liver, lungs, blood), while levels in other organs (brain, heart, kidneys) were below the detection limit.

Expression of the transgene was transient, with maximal levels observed between Days 3 and 7 post-administrations. Expression declined progressively and was undetectable within approximately 3–4 weeks.

Studies using a surrogate adenoviral construct expressing recombinant human lactoferrin demonstrated dose-dependent pharmacokinetics. Increased dose resulted in higher maximum concentration (Cmax) and area under the curve (AUC). Time to peak concentration was approximately 6.7 ± 0.4 days and was dose-independent. Protein levels declined over 30 days, with an estimated half-life of approximately 14 days.

Conclusion: Secondary pharmacodynamic data support a predictable, dose-dependent, and transient expression profile with limited systemic distribution, consistent with the expected behavior of non-replicating adenoviral vectors.

- **Safety Pharmacology:**

Safety pharmacology endpoints were evaluated as part of repeat-dose and single-dose toxicity studies in mice, rabbits, guinea pigs, and non-human primates (rhesus monkeys).

Summary of Safety Pharmacology Findings:

System / Parameter	Species	Assessment Method	Key Findings	Conclusion
Central Nervous System	Mice, Rabbits, Primates	Clinical observation (behavior, physical condition)	No abnormalities in behavior, neurological signs, or physical condition	No CNS toxicity observed
Cardiovascular System	Primates, Rodents	Clinical signs, body temperature, physiological monitoring)	No signs of cardiovascular dysfunction; stable vital parameters	No cardiovascular safety concerns
Respiratory System	Primates, Rodents	Clinical observation)	No respiratory distress or abnormalities observed	No respiratory safety concerns
General Toxicity	All species	Mortality, clinical signs, body weight, lab parameters	No mortality or systemic toxicity, no significant changes in body weight or labs	Well tolerated
Local Tolerance	Mice, Rabbits	Injection site observation (IM, IV)	No irritation or local adverse reactions	Good local tolerance
Immunotoxicity	Mice	DTH response, macrophage activity, antibody	No effects on immune function,	No immunotoxicity

		formation, lymphoid organ analysis	organ weight, or cellularity	
Allergenicity	Guinea pigs	General anaphylaxis tests	No hypersensitivity reactions detected	Non-allergenic
Non-Human Primate Safety	Rhesus monkeys	Clinical observation, lab parameters	No systemic toxicity, no local reactogenicity, no lab abnormalities	Safe at human equivalent dose

Conclusion: The safety pharmacology assessment indicates no adverse effects on vital organ systems, including central nervous, cardiovascular, and respiratory systems. The vaccine was well tolerated with no evidence of immunotoxicity or allergenicity.

B. Nonclinical pharmacokinetics

Pharmacokinetic studies are generally not applicable to vaccines. Therefore, no standard absorption, distribution, metabolism, and excretion (ADME) studies were conducted but pharmacokinetic characteristics were evaluated through biodistribution studies, vector clearance, and transgene expression analyses to support the mechanism of action and safety of the recombinant adenoviral vector.

Absorption and Distribution: Following administration, recombinant adenoviral vectors bind to high-affinity coxsackievirus and adenovirus receptors (CAR) and integrins on host cells. After entry into systemic circulation, virions are rapidly cleared, with an estimated half-life of approximately 1.5 hours.Cellular uptake occurs via receptor-mediated endocytosis, followed by intracellular trafficking and deproteinization. The vector genome persists as episomal DNA for a limited duration.

Quantitative PCR analysis following a single intramuscular administration demonstrated that the majority of adenoviral vector genomes were localized at the injection site (muscle tissue).

-At 6 hours post-dose, the highest concentration was detected in muscle tissue

-Limited distribution was observed in lymph nodes, spleen, liver, lungs, blood, and reproductive tissues

-No detectable levels were observed in the brain, heart, kidneys, urinary bladder, or gastrointestinal tract

Transgene Expression and Persistence: was assessed using reporter gene systems.

- Maximum expression observed between Days 3 and 7 post-administrations
- Expression declined progressively over time
- Expression levels were reduced to negligible levels within approximately 3–4 weeks

This profile reflects transient antigen production consistent with the non-replicating nature of the vector.

Model Protein Pharmacokinetics (Surrogate Analysis): Pharmacokinetics of expressed proteins were evaluated using a surrogate adenoviral construct encoding recombinant human lactoferrin (Ad-Lf).

-Dose-dependent increases in maximum concentration (Cmax) and area under the curve (AUC) were observed
-Time to maximum concentration (Tmax) was approximately 6.7 ± 0.4 days and independent of dose
-Protein levels increased up to Day 6, followed by a gradual decline over approximately 30 days
-Estimated half-life (t1/2) of the expressed protein was approximately 14 days
These findings demonstrate sustained but controlled systemic exposure to the expressed protein.

Elimination: Elimination of the vector occurs through rapid clearance from circulation and intracellular degradation following episomal persistence. The decline in transgene expression over 3–4 weeks reflects functional elimination of vector activity rather than classical metabolic clearance.

Conclusion: The pharmacokinetic profile of the recombinant adenoviral vector vaccine is characterized by:
-Rapid clearance from systemic circulation.
-Predominant localization at the injection site.
-Limited systemic biodistribution.
-Transient transgene expression.
-Predictable, dose-dependent protein expression kinetics.

C. Toxicology

The investigational product is a recombinant adenoviral vector vaccine (Ad26) encoding the SARS-CoV-2 spike protein, designed to induce both humoral and cellular immune responses. The vaccine is biotechnologically produced and does not contain live SARS-CoV-2 virus. The nonclinical safety program included:

- Single-dose toxicity studies:
    - Species: mice, rabbits, non-human primates
- Allergenicity studies:
    - Species: guinea pigs
- Immunotoxicity studies:
    - Species: mice

A placebo control group was included in all relevant studies.

➢ **Single-dose toxicity:**

Studies in Mice: Single-dose toxicity was evaluated in mice (n=400; both sexes) following intramuscular and intravenous administration of vaccine components at doses ranging from 10^8 to 10^{11} viral particles.

Observations:

-No mortality observed at any dose level.
-No clinical signs of toxicity: Normal behaviour, grooming, and activity and physiological functions.
-Body weight increased normally in all groups.

-No local irritation at injection sites.

Conclusion: No evidence of acute toxicity across the dose range, including supratherapeutic doses.

Studies in Non-Human Primates (Rhesus Macaques): Dose: 10^{11} v.p. (human therapeutic dose)

Schedule: Day 1: Component 1 and Day 21: Component 2.

Observation period: 28 days.

Observations

-Normal behaviour and physical condition.

-No local reactogenicity.

-No significant changes in Haematology and biochemistry.

Conclusion: The vaccine was well tolerated at the human dose, with no toxicological findings.

Studies in Common Marmosets (Callithrix jacchus): Dose: Full human dose (prime-boost).

Observations:

-No mortality or serious adverse effects.

-Increased motor activity with slight increase in body temperature (~0.9°C).

-No significant differences in: Haematological parameters, biochemical parameters.

Conclusion: Observed changes were consistent with expected pharmacological (immune) response and not indicative of toxicity.

- **Repeat-dose toxicity:**

Although formal repeated-dose toxicity studies were not conducted, the prime-boost regimen in rhesus macaques and marmosets provides supportive data for repeated exposure.

Observations:

-No cumulative toxicity following two sequential administrations.

-No target organ toxicity or progressive clinical abnormalities.

-Observed effects (e.g., lymphocyte increase, mild temperature rise) were transient and pharmacologically mediated (immune response).

Conclusion: Repeated administration in a prime-boost schedule did not result in cumulative or delayed toxicity, supporting the safety of the proposed clinical dosing regimen.

- **Allergenicity:**

Allergenicity of the recombinant adenoviral vector vaccine (Ad26 and Ad5 components) was evaluated in albino guinea pigs (n=60) using: General anaphylaxis test (systemic hypersensitivity) and Conjunctival test (local hypersensitivity).

Sensitization involved repeated administrations followed by a provocative (challenge) dose.

Results: For the systemic hypersensitivity (Anaphylaxis):
-No anaphylactic reactions observed following intracardiac challenge.
-Weigle index indicated absence of anaphylactic shock.
For the local hypersensitivity (Conjunctival Test):
-No immediate or delayed hypersensitivity reactions.
-No signs of redness, edema or irritation.
Conclusion: The vaccine demonstrated no allergenic potential, with no evidence of systemic or local hypersensitivity reactions under the conditions of the study.

- **Immunotoxicity:**

Immunotoxicity was evaluated in mice (F1 hybrids and inbred strains) following intramuscular administration pf 10^8 v.p. (effective dose) and 10^9 v.p. (10× dose). Two administrations, 21 days apart.
Endpoints assessed:

- Cell-mediated immunity (DTH)
- Macrophage phagocytic activity
- Humoral immune response (hemagglutination)
- Immune organ weight and cellularity

Results:

- Cell-Mediated Immunity (Delayed-Type Hypersensitivity: No significant differences in reaction index or edema, No induction of abnormal immune inflammation.
- Phagocytic Activity: No effect on peritoneal macrophage activity.
- Humoral Immune Response: No changes in antibody production (hemagglutination titers).
- Immune Organ Assessment: No impact on: Weight of thymus, spleen, lymph nodes.

Conclusion: No evidence of immunosuppression or immunostimulation outside expected pharmacological effects.
No adverse effects on cell-mediated immunity, humoral immunity or innate immune function. So overall, the vaccine showed no immunotoxic potential at therapeutic and supratherapeutic doses.

- **Summary of previous clinical studies:**

Study / Protocol	Phase / Design	Population (n)	Key Objective	Immunogenicity	Safety Summary	Key Conclusion
02-Gam-COVID-Vac-2020 (Stage I)	Phase I, open-label	18 (young adults, male)	Safety & immunogenicity	Strong humoral + cellular response	All AEs mild/moderat; no SAEs	Acceptable safety, immune response confirmed
02-Gam-COVID-Vac-2020 (Stage II)	Phase I/II, open-label	20	Safety & immunogenicity	Enhanced immune response vs stage I	Mostly mild AEs; no SAEs	Consistent safety, improved immunogenicity

02-Gam-COVID-Vac-2020 (Combined)	Phase I/II	38	Safety & immunogenicity	100% seroconversion (IgG)	No severe AEs; all recovered	Strong immune response, good tolerability
Prime-boost vs single dose analysis	Exploratory	Subgroup	Compare regimens	Higher titers in 2-dose regimen	Similar safety profile	Boosted regimen superior immunologically
05-Gam-COVID-Vac-2020 (>60 yrs)	Phase II, open-label	109	Safety in elderly	~98% seroconversion (Day 28)	Mostly mild AEs; 1 SAE (unrelated)	Effective and safe in elderly population
05-Gam-COVID-Vac-2020 (cellular immunity)	Phase II subset	Subgroup	Cellular immunity	CD4+ and CD8+ activation	No severe AEs	Strong cellular immune response
04-Gam-COVID-Vac-2020 (RESIST)	Phase III, randomize, placebo-controlled	12,296	Efficacy, safety	Strong immune response	No vaccine-related SAEs	High efficacy and good safety profile
04-Gam-COVID-Vac-2020 (Single dose – Component I)	Phase III analysis	Subgroup	Early protection	Rapid antibody response	Mild/moderate AEs	Effective as single-dose (Sputnik Light)

1) An Open-label study of safety, tolerability, and immunogenicity of Gam-COVID-Vac, a solution for intramuscular injection, in healthy volunteers

Study objective: To evaluate safety, tolerability, and immunogenicity of Gam-COVID-Vac, a solution for intramuscular injection, at various intervals after vaccinating healthy adult volunteers.

Phase: Phase I

Design: Open-label, non-randomized, two-stage, prospective study.

Population: Healthy adult volunteers.

Procedures steps: Hospitalization and isolation during observation.

Extensive safety and immunogenicity assessments including:

Hematology, biochemistry, immunology panels.

SARS-CoV-2 antibody titers (IgG, IgM).

Neutralizing antibodies.

Cell-mediated immunity (T-cell response, IFN-γ).

PCR testing for SARS-CoV-2.

ECG and vital signs monitoring.

Primary Endpoint: SARS-CoV-2 glycoprotein-specific antibody titers.

Secondary Endpoints: Seroconversion rate, neutralizing antibody titers and cell-mediated immune response: T-cell proliferation and IFN-γ production.

Clinical Observation: For Immunogenicity:

-Gam-COVID-Vac induced robust humoral and cellular immune responses.

-Prime-boost regimen demonstrated superior immunogenicity.

-Neutralizing antibodies reached 100% seroconversion by Day 42.

-Favourable safety profile as no SAEs or no severe AEs detected.

Conclusion: Gam-COVID-Vac, administered either as a single dose or in a prime-boost regimen, is safe, well tolerated, and highly immunogenic in healthy adults. The prime-boost regimen is superior and supports its use in subsequent clinical studies and clinical practice.

2) An open study of safety, reactogenicity, and immunogenicity of the vector vaccine against the Ebola fever, a solution for intramuscular administration at a dose of 0.5 ml in healthy volunteers.

Study objective: To assess safety, reactogenicity, and immunogenicity of the vector vaccine against Ebola fever, a solution for intramuscular administration at a dose of 0.5 ml in healthy volunteers.

Phase: Phase I/II.

Design: Open-label study.

Population: Total enrolled: 92 volunteers, Vaccinated: 72 volunteers, Backups: 20 (3 used during study)

Primary Endpoint: To measure GP-specific IgG antibody titers and safety and reactogenicity.

Secondary Endpoints: NP-specific antibody titers,Neutralizing antibodies and cell-mediated immunity: CD4+ and CD8+ T-cell proliferation and IFN-γ production.

Clinical Observation: For Immunogenicity:

-Vaccine induced strong humoral immunity and robust T-cell response.

-The full dose induced superior cellular immunity, higher IFN-γ response and broader NP-specific protection.

For Safety and Reactogenicity:

-Showed favourable safety profile as no SAEs detected with mostly mild expected vaccine-related reactions.

-Reactogenicity consistent with viral vector vaccines.

Conclusion: The GamEvac vector vaccine against Ebola demonstrates:

-Good safety and tolerability.

-Acceptable reactogenicity.

-Strong immunogenicity, including both humoral and cellular responses.

The full therapeutic dose (0.5 mL) provides superior immunological outcomes and is recommended for further use, particularly in high-risk populations.

3) **An open study of safety, reactogenicity, and immunogenicity on the "GamEvac vector vaccine against the Ebola fever" at a dose of 0.5 ml+0.5 ml in healthy volunteers**

Study objective: To evaluate the safety, reactogenicity, and immunogenicity of the combined vector Ebola vaccine (GamEvac-Combi) administered in a prime-boost regimen.

Phase: Phase I/II.

Design: Open-label study.

Population: Total enrolled: 92 volunteers, vaccinated: 84 volunteers, Backups: 8 (2 used during study).

Investigational product: GamEvac-Combi (combined vector vaccine).

Route: Intramuscular.

Dosing regimen (prime-boost): 0.5 mL + 0.5 mL (two-dose regimen).

Primary Endpoint: To measure GP-specific IgG antibody titers and safety and reactogenicity.

Secondary Endpoints: Neutralizing antibodies (VNA) and cell-mediated immunity:

CD4+ and CD8+ T-cell proliferation and IFN-γ production.

Clinical Observation: For Immunogenicity:

-Vaccine induced 100% seroconversion and strong humoral and cellular immunity.

-The full dose showed higher magnitude immune response and more consistent IFN-γ production.

For Safety and Reactogenicity:

No serious adverse events (SAEs) reported.

AEs classified as: Very frequent (≥10%) and Frequent (≥1% to <10%).

Conclusion: The findings obtained allowed putting the recommendation to use the drug "Gam-Evac-Combi, a combined vector vaccine for the prophylaxis of Ebola fever, 0.5 ml+0.5 ml/dose" for the prophylaxis of Ebola hemorrhagic fever as it's safe, well tolerated and highly immunogenic, inducing both humoral and cellular responses.

4) **"Double-blind randomized placebo-controlled studies on safety and immunogenicity for the drug Gam-Evac-Lyo, a vaccine for the prophylaxis of Ebola vector fever, a lyophilizate to prepare a solution for intramuscular injections"**

Study objective: To evaluate the safety, tolerability, and immunogenicity of GamEvac-Lyo in healthy adult volunteers.

Phase: Phase I–II.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Population: Screened: 253 volunteers, Randomized and treated: 220 volunteers:

- GamEvac-Lyo: 145
- Placebo: 75

Primary Endpoint: To measure GP-specific IgG antibody titers and safety and tolerability.

Secondary Endpoints: Neutralizing antibodies (VNA) and cell-mediated immunity: IFN-γ production.

Clinical Observation: For Immunogenicity:

GamEvac-Lyo induces:

- Very high seroconversion (~99%).
- Strong neutralizing antibody response.
- Robust T-cell immunity.
- Durable immune response.

For Safety and Tolerability:

No serious adverse events (SAEs) reported.

Mostly mild, transient AEs.

Conclusion: GamEvac-Lyo demonstrates:

-Favorable safety and tolerability profile.

-High immunogenicity, including both humoral and cellular responses.

-Clear superiority over placebo.

The vaccine meets WHO criteria for Ebola prophylactic vaccines and supports further clinical use with a positive benefit-risk profile.

5) "International multicenter immunogenicity study on the medicinal drug GamEvac-Combi, a combined vector vaccine against the Ebola virus disease, 0.5 ml + 0.5 ml per dose"

Study objective: To evaluate the safety, tolerability, and immunogenicity of GamEvac-Combi, a combined vector vaccine against the Ebola virus disease, 0.5 ml + 0.5 ml per dose.

Design: Randomized, double-blind, placebo-controlled.

Population: Vaccine group: 1,900 participants.
Placebo group: 100 participants.

Vaccine: GamEvac-Combi (combined vector Ebola vaccine).

Dosage regimen:

- Component A → Day 1
- Component B → Day 21

Dose: 0.5 ml per injection

Clinical Observation: For Immunogenicity:

Vaccine demonstrated:

-High immunogenicity across study populations.

Although detailed antibody values are not reported but findings align with earlier studies showing:

-Strong antibody response.

-Robust immune activation.

For Safety and Tolerability:

-Frequency and type of adverse events is consistent with known safety profile.

-No unexpected safety concerns reported.

Conclusion: GamEvac-Combi vaccine:

-Demonstrates good safety and tolerability.

-Shows high immunogenicity.

6) "A double-blind, placebo-controlled study with an open dosage selection period to assess safety and immunogenicity for the medicinal product "MERS-GamVac, a vector vaccine against the Middle East Respiratory Syndrome, a lyophilizate to prepare a solution for intramuscular injections", involving healthy volunteers"

Study objective: To assess safety, reactogenicity, and immunogenicity of MERS-GamVac, a vector vaccine against the Middle East Respiratory Syndrome in healthy volunteers.

Design: Randomized, double-blind, placebo-controlled.

Target population: Healthy adults (18–55 years)

Stage 1: 40 volunteers
Stage 2 (planned): 122 volunteers

- 88 vaccine
- 34 placebo

Clinical Observation:

For Immunogenicity:

1-Humoral Immunity (IgG antibodies)

Response against MERS-CoV S protein

Dose	Seroconversion	Antibody Level (Day 42 peak)
Half dose	90%	~1048
Full dose	100%	~1970

2- Neutralizing Antibodies (VNA)

Detectable at ≥1:20 titer

Time	Half Dose	Full Dose
Day 14	60%	70%
Day 28	80%	100%

3- Cellular Immunity (T-cell response)

Measured via IFN-γ production + T-cell proliferation

Response Type	Half Dose	Full Dose
CD4+ response	90%	~95%
CD8+ response	75%	~95%

For Safety and Reactogenicity:

-No clinically significant changes in vital signs (BP, HR, RR, temperature), ECG and laboratory parameters (blood, urine, biochemistry)

-Some statistically significant differences observed:

- Considered false positives (Type I errors)
- Values remained within normal ranges

Conclusion: MERS-GamVac vaccine shows:

-Favorable safety profile with good tolerability and strong immunogenicity.

-Full dose is preferred due to higher antibody levels, better neutralization, stronger T-cell response and similar safety to half dose.

-Recommended to use full dose in further clinical stages.

7) "Open-label Dose-escalation Study of Safety, Reactogenicity, and Immunogenicity of GamFluVac, an Influenza A Vector Vaccine, in 3 Groups of healthy volunteers"

Study objective: To Assess safety, reactogenicity and preliminary immunogenicity of GamFluVac in 3 Groups of healthy volunteers**.**

Phase: Phase I study.

Design: Open-label, dose-escalation Phase I study.

Dosing: Single dose, 3 escalating dose groups.

Population: Total enrolled: 41 volunteers (including 5 backups), Vaccinated: 36 volunteers.

Clinical Observation: For Immunogenicity:

1 .Humoral Immune Response (Antibodies)

-Significant increase in influenza A antibodies with dose-dependent effect.

-Highest response in Group 3 (highest dose).

2 .Cell-Mediated Immunity

-Strong response observed mainly in highest dose group:

Increased CD8+ T-cell proliferation

Increased IFN-γ production

-CD4+ response was not significantly changed.

3 .Methods Insight

ELISPOT not sensitive enough.

Better methods: Lymphoproliferation assays and IFN-γ measurement.

For Safety and Reactogenicity:

-Showed favourable safety profile with no serious or unexpected risks.

Conclusion: GamFluVac is safe and well tolerated in healthy adults showing:

-No serious adverse events observed.

-Immune response is dose-dependent, strongest at highest dose.

-Laboratory changes reflect normal immune activation, not pathology.

-Vaccine shows promising immunogenicity.

So it's recommended for further clinical development (Phase II).

8) "Double-blind, Placebo-controlled Study with an Open Dose Selection Period for Assessing the Safety and Immunogenicity of the MERS-GamVac-Combi Drug, Combined Middle East Respiratory Syndrome Vector Vaccine, Lyophilizate for Intramuscular Injections, in Healthy Volunteers"

Study objective: To assess safety, Tolerability , and immunogenicity of MERS-GamVac-Combi vaccine (vector-based MERS vaccine) against the Middle East Respiratory Syndrome in healthy volunteers.
Design: Randomized, double-blind, placebo-controlled with open dose-ranging phase.
Participants: 268 healthy adults (18–55 years, both sexes**)**
Stages:

- Stage 1: 80 participants (+8 backups)
- Stage 2: 188 participants: 138 vaccine and 50 placebo

Clinical Observation:
For Immunogenicity:
1-Humoral Immunity (antibodies)
After Component 1: Strong antibody response to MERS-CoV S protein.

Dose	Seroconversion
Half dose	90%
Full dose	95%

After Both Components

Dose	Seroconversion	Antibody Level (Day 35 peak)
Half dose	90%	~13,825
Full dose	100%	~18,740

2- Neutralizing Antibodies (VNA)
Increased over time being higher in full-dose group.
Up to 95% of participants reached protective titers.
3- Cellular Immunity (T-cell response)
Measured via IFN-γ production + T-cell proliferation

Response Type	Half Dose	Full Dose
CD4+ response	moderate response	~80%
CD8+ response	moderate response	~70%

For Safety and Reactogenicity:
-No clinically significant safety concerns.
-AEs mostly mild and transient.
-Well tolerated at both dose levels.
Conclusion: The vaccine meets WHO expectation (~70% protection threshold via immunogenicity).
The vaccine is safe, well tolerated and immunogenic with being the full dose is the optimal regimen.

9) Experience in the human use of "Gam-COVID-Vac Combined vector vaccine to prevent coronavirus infection caused by the SARS-CoV-2 virus", the component 1 of which corresponds to "Sputnik Light»

Study objective: To Evaluate efficacy, immunogenicity, and safety of Gam-COVID-Vac to prevent coronavirus infection caused by the SARS-CoV-2 virus.

Phase: Phase III

Design: Randomized, double-blind, placebo-controlled, multicenter.

Population: Screened: 12,296 adults (18–87 years)

Dose Regimen: Two-dose regimen (Component I + Component II, 21 days apart)

Dose: 1×10^{11} viral particles per injection and Control: Placebo

Clinical Observation: For Immunogenicity:

-Vaccine induces protective immunity against SARS-CoV-2 with strong humoral + cellular immune response.

-Vaccine shows %96 efficacy with significant reduction in: Infection risk and disease severity.

-Single Dose (Component I / Sputnik Light) demonstrates early protection even before second dose with %70 efficacy from Day 14 to day 20.

For Safety and Tolerability:

The vaccine shows good safety profile with no unexpected adverse events.

Similar safety in elderly vs general population.

AEs consistent with typical vaccine reactions.

Conclusion: The Gam-COVID-Vac vaccine demonstrates:

-High efficacy (~96%) in preventing COVID-19.

-Reduced disease severity in vaccinated individuals.

-Single-dose (Sputnik Light) provides early protection (~70%).

-No significant impact of age, gender, or comorbidities on efficacy.

-Strong immune response (humoral and cellular).

-Favorable safety profile with no vaccine-related serious risks.

- **Protocol:** A Phase III, Randomized, Double Blind, Placebo-Controlled International Multisite Clinical Trial in Parallel Assignment to Evaluate Efficacy, Immunogenicity and Safety of the Sputnik Light Vector Vaccine in Adults in the SARS-CoV-2 Infection Prophylactic Treatment.

  Phase: Phase III

- The **Sputnik-Light** is a single component vaccine based on human adenovirus serotype 26 that carries the SARS-CoV-2 virus S protein gene. The used recombinant particles based on pseudo-adenovirus particles ensure the synthesis of the SARS-CoV-2 S protein in human cells. Drugs based on recombinant pseudo-adenovirus particles used as vectors to deliver genetic information to human cells have proved its safety and efficacy in numerous clinical studies.

Objective(s):

Primary Objectives	Secondary Objectives
1. Assess efficacy of the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection compared to placebo. 2. Assess tolerability and safety of the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection compared to placebo.	1. Assess humoral immunogenicity of the Sputnik-Light vector vaccine against the SARS-CoV-2 induced coronavirus infection compared to placebo on Subset A which consists of 1076 participants. 2. Assess protective properties of the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection compared to placebo for prevention of serologically confirmed SARS-CoV-2 infection. 3. Assess efficacy of the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection compared to placebo based on severity of COVID-19 disease.

Endpoint(s):

Primary Endpoints	1. Proportion of study subjects with active COVID-19 disease developed at the day 21 after vaccination with the Sputnik-Light vector vaccine as compared with placebo. 2. Incidence and severity of adverse events in trial subjects: a. Incidence of local and systemic reactions to the vaccine in 7 days after injection with vaccine/placebo b. Incidence and severity of AEs and SAEs, over the course of subject's participation in the study
Secondary Endpoints	1. Humoral immunogenicity induced by the vaccine resulting in increase in the Quantitative IgG antibodies

		to SARS-CoV-2 S Protein in trial subjects (Subset A, 1 076 Subjects) a. Geometric mean titer (GMT) levels of Quantitative IgG antibodies to S Protein from baseline levels at Visit 1 (vaccination day, prior to injecting the first dose of the study vaccine/placebo) to Visit 2 (Day 42) and Visit 3 (Day 180) after injection with vaccine/placebo b. Percentage of trial subjects with four-fold or more increase in the titers of Quantitative IgG antibodies to S Protein from baseline levels at Visit 1 (vaccination day, prior to injecting the first dose of the study vaccine/placebo) to to Visit 2 (Day 42) and Visit 3 (Day 180) after injection with vaccine/placebo c. Percentage of trial subjects with seroconversion to SARS-CoV-2 S Protein from baseline levels at Visit 1 (vaccination day, prior to injecting the first dose of the study vaccine/placebo) to Visit 2 (Day 42) and Visit 3 (Day 180) after injection with vaccine/placebo d. Immunogenicity of the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection compared to placebo for the levels of virus-neutralizing antibodies compared at baseline (Visit 1), to Visit 2 (Day 42) and Visit 3 (Day 180) after injection with vaccine/placebo 2. Percentage of trial subjects who have a post-treatment response as measures with Qualitative IgG SARS-CoV-2 N-antibodies at Visit 2 (Day 42), and Visit 3 (Day 180) after injection with vaccine/placebo 3. Percentage of trial subjects with severe and extremely severe COVID-19 disease that developed after vaccination with Sputnik Light compared to placebo.

Rationale: The available data on the safety and immunogenicity of the study vaccine Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection allows considering highly protective and

safe properties of this candidate vaccine as a drug, the potential benefit of which significantly outweighs the risk. In an unfavorable epidemiological setting, it is expected that subjects will benefit from participating in the study. The risk of the disease developing, the clinical evidence, and peculiarities of the progression of the disease to date, there has been relatively limited information on epidemiology, clinical features, prevention, and treatment of this disease. It is known that the most common symptom of the novel coronavirus infection is bilateral pneumonia; acute respiratory distress syndrome (ARDS) has also occurred in 3–4% of subjects.

Design: Multi-country, Randomized, double-blind (blinded for the trial subject and the study physician), placebo-controlled trial in the parallel assignment of the immunogenicity, and safety of the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection in adults in the SARS-CoV-2 infection prophylactic treatment.

The trial will include up to 6000 subjects aged 18+. After screening, they will be randomized (1:3) into two groups – a reference group of up to 1500 subjects receiving placebo and a study group of 4500 subjects receiving the Sputnik-Light vector vaccine against the SARS-CoV-2-induced coronavirus infection. Randomization will be done with age stratification as follows: 18-30 years old., 31 – 60 years old., and 60 years old and older.

A share of the subjects completing the study prematurely after randomization is expected to be minimal.

Study Duration: Each subject will participate in the trial for up to 7 days at screening and up to 180±14 days from the first dose of the study vaccine/placebo and will have one screening visit and at least three onsite visits to the study physician over the course of the study. The study vaccine/placebo will be administered intramuscularly during vaccination Visit 1 (Day 1). Subsequent observation visits 2 & 3 will be performed on days 42±4, and 180±14 respectively. During the observation visits, vitals as well as changes in the subjects' condition and wellbeing compared to the previous visit will be recorded. Additionally, the trial subjects will be able to have remote consultations with the study physician through Tele-Consultation &/ or Phone Call.

In the following subsets of subjects additional blood samples will be taken:

• Subset A, 1076 volunteers: blood samples will be taken for quantitative IgG antibodies to S Protein and qualitative IgG and IgM antibodies to N protein

• Subset B, 300 volunteers (Russia only, included in Subset A): blood samples will be taken from subjects to assess virus neutralizing antibodies.

Blood sampling for immunogenicity parameters assessment will be carried out locally in the investigational sites.

Trial subjects' data will be collected using electronic case report forms and electronic diaries to be filled by trial subjects.
Clinical Laboratory: All required samples will be processed and analyzed locally including safety and analytical labs.
Three interim analyses are planned when the cumulative number of cases reaches 17%, 75% and 100%, i.e. 20, 85 and 113 cases respectively. Interim analyses results will be submitted to Data and Safety Management Board (DSMB).
Preliminary stop of the clinical study with statistical determination of early efficacy based on results of the interim report is not planned and the study will continue until the final completion of the protocol.
Early stop of the study, the study can be stopped only at decision of the Sponsor or DSMB.

- ***Recommendation &/ or*** **Questions & Answers:**

EDA Comment(s)	Applicant Reply
Q1: Although Sputnik V (containing component 26) has not elicited a satisfactory immune response after its administration, it is selected for clinical trials in Sputnik Light. Please, explain this crucial point.	**Regarding Sputnik V Vaccine Efficacy:** Sputnik V coronavirus vaccine gives around 92% protection against Covid-19, late-stage trial results published in The Lancet revealed. It has also been deemed to be safe - and offers complete protection against hospitalization and death. The vaccine was initially met with some controversy after being rolled out before the final trial data had been released. But now it's said that Sputnik V vaccine benefits outweigh its Risks besides it got EUA in Many countries UAE, Russia, Argentina, Hungary, Ghana, and other countries (including Egypt). **Sputnik light is one component I of the Sputnik V vaccine** which was tested for its effectiveness and safety in Phase I-II study that shows that the vaccine was well-tolerated and a single-shot immunization with Sputnik Light can cause the formation of a strong antigen-specific cell immunity as part of overall anti-infection immunity in volunteers. (Please refer to the attached Phase I-II study report for your reference). **For the proposed trial,** Testing the sputnik light vaccine in different groups ethnicity and larger sample

		size (6000 subjects) will obtain the most reliable efficacy and safety.

• **Abbreviation**:

ADME: Absorption, Distribution, Metabolism, Excretion
Ad26: Adenovirus serotype 26
Ad5: Adenovirus serotype 5
AE(s): Adverse Event(s)
ARDS: Acute Respiratory Distress Syndrome
AUC: Area Under the Curve
BP: Blood Pressure
CAR: Coxsackievirus and Adenovirus Receptor
CD4+: Cluster of Differentiation 4 positive T cells
CD8+: Cluster of Differentiation 8 positive T cells
CDC: Centers for Disease Control
Cmax: Maximum concentration
CNS: Central Nervous System
COVID-19: Coronavirus Disease 2019
DNA: Deoxyribonucleic Acid
DSMB: Data and Safety Monitoring Board
DTH: Delayed-Type Hypersensitivity
ECG: Electrocardiogram
EDA: Egyptian Drug Authority
ELISPOT: Enzyme-Linked ImmunoSpot assay
EUA: Emergency Use Authorization
FGBU: Federal State Budgetary Institution
HR: Heart Rate
IB: Investigator's Brochure
IFN-γ: Interferon gamma
IgG: Immunoglobulin G
IgM: Immunoglobulin M
n: number of participants / sample size
PCR: Polymerase Chain Reaction

PI(s): Principal Investigator(s)
qPCR: Quantitative Polymerase Chain Reaction
RR: Respiratory Rate
SAE(s): Serious Adverse Event(s)
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
Tmax: Time to maximum concentration
t1/2: Half-life
v.p.: Viral particles
VNA: Virus Neutralizing Antibodies
WHO: World Health Organization