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Safety and Immunogenicity of single dose of Sputnik light vaccine for prevention of SARS-CoV-2 Infection in Indian adults and elderly population - An open label, phase III, uncontrolled, multicentre study

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Abstract

Background: Sputnik Light (component I of Sputnik V) is a single-dose vaccine against COVID-19. It is approved in 28 countries for primary vaccination and as a booster in 14 countries. The results from Phase II/III trials conducted in Russia have demonstrated efficacy, safety, and immunogenicity of Sputnik light vaccine. Recently, the Drugs Controller General of India (DCGI) has granted emergency-use permission to the single-dose Sputnik Light COVID-19 vaccine in India based on the interim results of Phase III immunogenicity and safety study conducted in Indian adults and elderly population for prevention of SARS-CoV-2 Infection. This report presents the Day 90 interim immunogenicity analysis results and safety data up to Day 42 from the Phase III India study. The trial is registered on CTRI, and the registration no. is CTRI/2021/09/036830.

Methods: This was an open label, phase III, uncontrolled, multicentre, study to evaluate immunogenicity and safety of single dose of Sputnik light in Indian adults and elderly for prevention of SARS-CoV-2 Infection. Primary outcome measure was geometric mean titres (GMT) of glycoprotein specific antibodies at Day 42, 90 and 180. Secondary outcome measures were GMTs of glycoprotein specific antibodies at Day28; GMTs of virus neutralising antibodies (VNA) and seroconversion rates for glycoprotein specific antibodies and VNA at Day 28, 42, 90 and 180; and safety as well as incidence, severity, and outcome of COVID-19 disease in subjects who received sputnik light.

Results: Of the 179 subjects enrolled into the study, 144 (80.4%) subjects were male and 35 (19.6%) were female. The mean (±SD) age of the study subjects was 30 ± 9.5 years. Approx. 86% of subjects were seropositive at baseline. Post vaccination, the GMT values of glycoprotein specific antibodies continued to increase up to Day 90 and showed a 14-fold, 33-fold and 46-fold increase at Day 28, 42 and 90, respectively from baseline titres of 888.47. VNA titres peaked by approx. 7-fold at Day 28 and thereafter it plateaued at approx. 4.5-5-fold rise at Day 42 and 90 compared to baseline titres of 51.93. Similar trend of increase in immunogenicity titres was seen in subjects irrespective of their baseline serostatus. All the baseline seronegative subjects (N=25) seroconverted for glycoprotein specific antibodies post vaccination whereas approx. 70% of baseline seronegative subjects were seroconverted at Day 90 for VNA. A total of 90 Adverse Events (AEs) were reported in 60 (33.5%) subjects of which 84 (93.3%) were mild and 6 (6.7%) were moderate. No Serious Adverse Events were reported till Day 42. No cases of COVID-19 infection were reported in the study.

Conclusion: Based on the interim analysis results, single-dose of rAd26 vector-based COVID-19 vaccine "Sputnik Light" was found to be safe and well tolerated in Indian subjects and demonstrated adequate immune response in all subjects irrespective of their baseline serostatus.

Keywords: COVID-19, Sputnik light, Receptor-Binding Domain, Immunogenicity, SARS-CoV-2 glycoproteins specific antibodies, Seroconversion, and Virus neutralizing antibodies.

Introduction

In the 2nd week of December 2019, it all started with China reporting gradual rise in cases of atypical pneumonia in the city of Wuhan, which was found to be caused by a novel corona virus SARS-COV-2 (severe acute respiratory syndrome) [1-2]. WHO (under International Health Regulations) has declared this outbreak as a "Public Health Emergency of International Concern" (PHEIC) on 30th January 2020, and subsequently declared this scenario as a pandemic on 11th March 2020 [3]. Ever since the COVID-19 pandemic was declared, more than 410 million cases and 5.8 million disease-associated deaths have been reported worldwide and these numbers are still continuously growing [4]. The rapid spread of this infection, as well as the increasing number of severe cases (with high mortality rate), emphasize the need for vaccine research and development [5]. COVID-19 vaccination campaign has been launched around the world. More than 10 billion doses have been administered, according to the WHO Coronavirus (COVID-19) Dashboard [6]. Published studies shows that vaccination reduces the number of COVID-19 cases and dramatically reduces

COVID-19-associated hospitalizations and deaths worldwide [7]. The sudden emergence of SARS-CoV-2 virus and its rapid spread with high morbidity and mortality called for extraordinary efforts in the field of vaccine development that led to the registration of several vaccines licensed for emergency use by the end of 2021 [8].

"Sputnik Light" a single dose vaccine [Recombinant adenovirus serotype 26 particles containing the SARS-CoV-2 protein S gene], was developed by Human LLC to boost the global immunisation rate against the SARSCoV-2 infection [9]. The Phase I/II Clinical trials conducted by Gamaleya Research Institute demonstrated that, post vaccination significant levels of SARS-CoV-2 virus S protein RBD domain-specific IgG antibodies (titre higher than 1:50) were detected in 98.1% of volunteers on day 28 and exhibited a rise in the VNA levels on the 28th day and exhibited constant levels throughout the study [10]. And the results from phase III clinical trial demonstrated that Sputnik Light vaccine provides efficacy of 65.4% against COVID-19, 21 days after immunization [11].

A single-dose COVID-19 vaccine, we believe, will increase the portfolio of licenced COVID-19 vaccines, adding to the vaccine supply needed to achieve population immunity on a national and worldwide scale. Here we report interim results of immunogenicity (up to Day 90) and safety (up to Day 42) of “sputnik light” vaccine in 179 subjects aged 18-60 years.

Methods

Study Design & Participants

We are conducting this ongoing Phase III, open label, un-controlled, multicenter study to evaluate immunogenicity and safety of single dose of Sputnik Light [Recombinant adenovirus serotype 26 particles containing the SARS-CoV-2 protein S gene] in Indian adults and elderly for prevention of SARS-CoV-2 Infection. This study was conducted at 5 different sites all over India, with 179 enrolled subjects after obtaining their written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by DCGI and the ethics committee of the clinical sites. The trial is registered on CTRI, and the registration no. is CTRI/2021/09/036830.

Eligibility criteria were age 18 years or more, negative COVID-19 RT-PCR test result and IgM SARS specific antibodies at the screening visit; No, medical history of COVID-19 in past 90 days; Consent to use effective contraceptive methods during and after 3 months of trial; No history of any reactions or complications after receiving a vaccine or immunological products; No history of acute infection and/or respiratory disease within at least 14 days before the enrollment.

Key exclusion Criteria were any vaccination/ immunization within 30 days or against COVID 19 before the enrolment; any ongoing steroids/ immunoglobulins/ blood products therapy in the last 30 days before enrolment; immunosuppressive therapy within 3 months before enrolment; neutropenia or severe anemia, in screening test; immunodeficiency or autoimmune disorders in the medical history within 6months before the enrolment. Patient enrolment was done during 01 Oct 2021 to 06 Oct 2021. Vaccinated subjects were followed up to 6 months (180 days). The subject disposition and study overview is depicted in Figure 1.

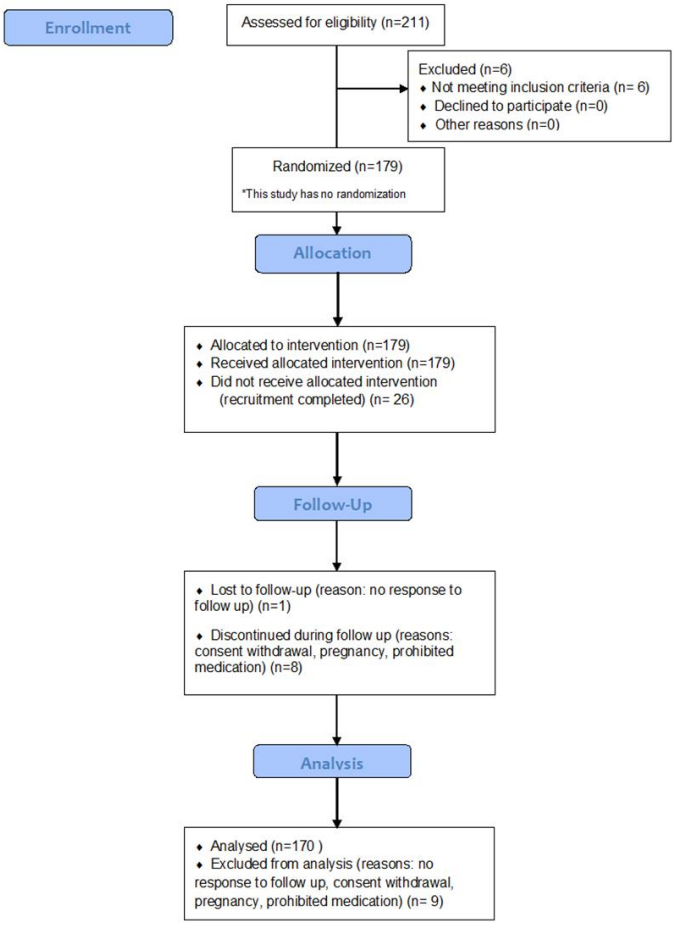

Figure 1: Diagram illustrating patient disposition and study overview.

Procedures

On screening visit, all the subjects who signed the informed consent document were evaluated by Investigator and data pertaining to demographics and medical history was collected. Physical examination, vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature), laboratory tests for safety assessments and blood test for detection of HIV, hepatitis B and hepatitis C were also done. SARS-COV-2 RT-PCR test for all the subjects was done, by collecting their nose/throat swabs, and patients with COVID-19 were excluded.

The Intended duration of participation of each subject in the study is 180 days, from vaccination day. A screening visit and six on-site visits to the clinical site were scheduled for each subject throughout the trial.

Single dose of 0.5 ml solution containing Sputnik light (Recombinant vector based on the human adenovirus serotype 26 particles containing the SARS-CoV-2 protein S gene, in the amount of $(1.0\pm0.5) \times 10^{11}$ particles per dose (Component 1 of Gam COVID-VAC Vaccine i.e., Sputnik V)) was administered intramuscularly to 179 subjects, enrolled into the study on vaccination visit i.e., Day 1.

On the subsequent observation visits Day 28, Day 42, Day 90, and Day 180 (End of Study): vital signs were assessed in all trial participants and changes in the participants condition and wellbeing compared with the previous visit were recorded. Concomitant medications used and AEs encountered by subjects were recorded in the eCRF for all the visits.

Blood samples were collected from the trial participants just before the study drug administration. Collected blood samples were assayed for safety and immunogenicity parameters. The titer of SARS-CoV-2 glycoprotein-specific antibodies in serum was ascertained by ELISA (High-sensitive SARS-CoV-2 S1RBD IgG ELISA Kit, invented by Toronto bioscience was used) on the day of vaccination and day 28, 42, 90 and 180. To determine the VNA, assays were done on the day of vaccination and day 28, 42, 90 and 180.

Outcomes

Primary outcome measure was geometric mean titers (GMT) of glycoprotein specific antibodies at Day 42, 90 and 180. Secondary outcome measures were GMTs of glycoprotein specific antibodies at Day28; GMTs of VNA and seroconversion rates for glycoprotein specific antibodies and VNA at Day 28, 42, 90 and 180; AEs reported within 7 days of vaccination and day 8 to day

180; and incidence, severity, and outcome of COVID-19 disease in study subjects till the end of the study.

Sample size calculation

For this single arm immunogenicity study, the sample size was calculated to test the hypothesis that the GMT for SARS-Cov-2 glycoprotein specific antibody in vaccine arm would be non-inferior as comparing the GMT at Day 42 with the results of Russian I/II and Phase III of Sputnik Light (GMT at Day 42 are 2285.0 in Phase I/II Russia study and 4762.2 in Phase III Russia study). The true GMT ratio and CV were taken as 1 and 2.2 (SD of log transformed titre at Day 42=1.33), respectively. An estimated sample size of 143 for overall immunogenicity assessment will give 90% power at 5% level of significance to test the 30% non- inferiority margin i.e., non-inferiority will be assessed when the lower limit of 95% CI of GMT ratio will be ≥ 0.7. Considering 20% dropouts the sample size was 179.

Statistical analysis

All the statistical calculations were done in statistical software "SAS®" version 9.4 or higher (SAS Institute Inc, Cary, North Carolina). Reported AEs were coded in accordance with MedDRA version 23.0. We used t-test to compare the log transformed values of SARS-CoV-2 glycoprotein-specific antibodies titers at day 42 & 90. Seroconversion rate (4-fold rise from baseline) of SARS-CoV-2 VNA on days 28, 42 & 90 were calculated with 95% CI using Clopper-Pearson's method. The frequency and percentage of hospitalization, death, recovery without hospitalization due to COVID-19 were calculated with 95% CI using Clopper-Pearson method.

Results

Of the 179 subjects, 144 (80.4%) subjects were male and rest 35 (19.6%) were female. All the subjects were of Asian ethnicity. Overall Mean ± SD age, weight (Kg), height (cm) and BMI (kg/m2) of subjects was 30.0 ± 9.55 years, 63.2 ± 9.99 kg, 165.8 ± 7.27 cm and 23.0 ± 3.79, respectively. **(Table 1)**

Table 1: Summary of Subject Demography- Safety Analysis Set (N=179)

Parameter	Statistic/Category, n (%)	Total ((N=179)
	N	179
	Mean	30.0
	SD	9.55
	Median	28.0
	Range (Min: Max)	(18.0:69.0)
Age Group	<60 Years	174 (97.2%)
	60 Years and above	5 (2.8%)
Race	Asian	179 (100.0%)
	Other Specify	0 (0.0%)
Gender	Male	144 (80.4%)
	Female	35 (19.6%)
Height (cm)	n	179
	Mean	165.8
	SD	7.27
	Median	165.4
	Range (Min: Max)	(142.5:185.4)
Weight (Kg)	n	179
	Mean	63.2
	SD	9.99
	Median	62.4
	Range (Min: Max)	(42.7:104.2)
BMI (kg/m2)	n	179
	Mean	23.0
	SD	3.79
	Median	22.5
	Range (Min: Max)	(15.3:39.7)

Vaccination of all 179 subjects with sputnik light has shown a significant increase in SARS-CoV-2 glycoprotein specific antibodies throughout the study, a 13-fold increase on day 28 and a 32-fold increase on day

42 to a 46-fold on day 90. Similar trend was seen when further analysis was done on baseline seronegative and seropositive population. (Table 2)

Table 2. Summary of GMT values of SARS-Co-2 Glycoprotein specific antibodies in total population, seronegative and seropositive groups

Visit	GMT value (n=179)	Seronegative (n=25)	Seropositive (n=154)
Day 1	888.47	1.00	2974.36
Day 28	12423.19	3929.40	15012.55
Day 42	29045.97	15555.59	32187.79
Day 90	40834.24	30315	42809.91

After vaccination, by day 90 all the subjects in seronegative group are seroconverted 100% (23/23), whereas 62.9% (119/154) of all subjects from seropositive group were seroconverted. The total seroconversion rate for SARS-CoV-2 glycoprotein specific antibody was 58.8 % (104/ 179) on day 28, 80% (143/179) on day 42 and 79.3% (142/179) on day 90. (Table 3)

Table 3. Summary of SARS-CoV-2 glycoprotein specific antibodies seroconversion rates of total population, seronegative and seropositive groups

Visit	n	Seronegative	n	Seropositive	Total population (n=179)
Day 28	25/25	100%	79/154	52%	58.8%
Day 42	23/23	100%	118/154	77.6%	80%
Day 90	23/23	100%	119/154	69.2%	79.3%

For analysis of VNA, At Day 1, GMT (95% CI) was calculated to be 51.75 which increased to almost 7-fold by Day 28, then reached plateau by Day 42 and the same trend was maintained on Day 90. Similar trend was seen for baseline seronegative and seropositive population. (Table 4)

Table 4. Summary of VNA seroconversion rates of total population, seronegative and seropositive groups

Table 4. Summary of VNA seroconversion rates					
Visit	n	Seronegative	n	Seropositive	Total population (n=179)
Day 28	16/25	72.7%	87/154	61.7%	63.2%
Day 42	12/25	52.2%	82/154	54.7%	54.3%
Day 90	16/25	69.6%	81/154	55.54%	57.4%

The whole group of participants showed 63.2% (103/ 179), 54.3% (94/ 179) and 57.4% (97/ 179) seroconversion on day 28, day 42 and day 90 respectively. Seroconversion rate in seronegative vaccine recipients reached 69.6 % (16/25) by day 90. In seropositive group, by day 90, the seroconversion rate reached to 55.5% (81/154)]. (Table 5)

Table 5: Summary of GMT values of VNA in total population, seronegative and seropositive groups

Visit	GMT value (n=175)	Seronegative (n=23)	Seropositive (n=152)
Day 1	51.75	8.60	67.89
Day 28	368.50	109.63	438.32
Day 42	242.32	57.43	294.46
Day 90	251.93	87.57	295.19

Thus, Immunogenicity data at Day 90 suggests that single dose of Sputnik light vaccine provides effective titers of S-glycoprotein specific antibodies and VNA even at Day 90 post vaccination.

In terms of interim safety outcomes (Day 42), a total of 90 AEs were reported in 60 subjects (33.5%) (Reported in the EDC till November 22, 2021). Of which 69 AEs were reported by day 7 post vaccination and the other 21 AEs were reported in between day 8-42 post vaccination. 84 AEs of the reported 90 AEs were mild in intensity, and the rest 6 AEs were moderate in intensity. Out of the 90 AEs, relationship of 24 AEs was “Definite” or “certain”, 36 AEs was “unrelated” or “not related” and

the other 30 AEs relationship to the vaccine is "probable". No action was required for any of the 90 AEs reported in 60 (33.5%) subjects and all the AEs were completely resolved. (Table 6)

Table 6: Summary of most common AEs by SOC and PT – Safety Analysis Set (N=179)

SOC/PT, n (%) E [1] [2]	Overall(N=179)
Overall	60 (33.5%) [90]
Most common AEs reported	
General disorders and administration site conditions	51 (28.5%) [72]
• Asthenia	6 (3.4%) [6]
• Chills	3 (1.7%) [3]
• Injection site pain	29 (16.2%) [29]
• Malaise	2 (1.1%) [2]
• Pyrexia	26 (14.5%) [28]
• Vaccination site swelling	2 (1.1%) [2]
Musculoskeletal and connective tissue disorders	8 (4.5%) [8]
• Arthralgia	1 (0.6%) [1]
• Myalgia	6 (3.4%) [6]
Nervous system disorders	5 (2.8%) [5]
• Dizziness	1 (0.6%) [1]
• Headache	4 (2.2%) [4]
Respiratory, thoracic, and mediastinal disorders	2 (1.1%) [2]
• Cough	2 (1.1%) [2]

Discussions

More than 400 million people all over the world were infected with SARS-CoV-2 within a year of it being declared as a global pandemic and more than 5 million had died of the resulting pneumonia and systemic illness [12]. Antiviral and immunomodulatory therapies advanced swiftly, and preventive measures such as the use of convalescent serum, immune globulins, and monoclonal antibodies were attempted [13]. Despite of these efforts, no drug has been proven to be completely effective in treating COVID-19 disease, as number of new variants of corona virus are emerging, making the available treatment options ineffective. COVID-19 vaccination has been proved to be the only means/most effective measure to bring an end to this pandemic. To boost the vaccination campaign in India, we are conducting this clinical trial, whose outcome will define the availability of this single dose sputnik light vaccine to Indian population. Here, we report an interim analysis (Day 90 data) results of immunogenicity and safety from an open label, phase III, un-controlled, multicentre clinical trial in Indian population.

In Subjects (both seronegative & seropositive) vaccinated with sputnik light, there is a significant change in immunogenic properties from baseline to day 90. The baseline SARS-CoV-2 glycoprotein specific antibodies GMT values were amplified from 888.47 to a 46-fold increase by the end of day 90, indicating that participants have exhibited increased levels of antibodies against S-glycoprotein even after a period of 3 months post vaccination and the same trend is expected throughout the study period. We also found that a single dose of sputnik light vaccine has stimulated noteworthy increase in SARS-CoV-2 glycoprotein specific antibodies in seronegative subjects (subjects with no history of COVID-19 infection, at baseline) and a 1.4-fold greater increase was observed in seropositive subjects when compared to that of seronegative subjects by day 90(subjects with pre-existing immunity against COVID-19, at baseline). The level of virus neutralising antibodies has recently been proved to be a highly

predictive indication of immunological protection against COVID-19 [14]. A 5-fold increase in VNA was observed from baseline to day 90. Vaccination with "Sputnik light" led to a 3.3-fold increase in VNA GMT levels of seropositive group, in comparison with seronegative group at day 90. Assessment of SARS-CoV-2 glycoprotein titres till day 90, revealed that the seroconversion rate reached 100% (23/23) in seronegative group. At the same time, in the seropositive group, seroconversion rate was 62.9% (119/ 154). Analysis of VNA to SARS-CoV-2 showed 69.6% (16/25) and 55.5% (81/154) seroconversion rates by day 90 in the seronegative and seropositive groups, respectively.

In terms of safety outcome, we found that single dose "sputnik light" vaccine was well tolerated in seronegative and seropositive participants. The most common adverse effect reported was injection site pain in 29 (16.2 %) subjects, followed by 28 events of pyrexia in 26 (14.5 %) subjects, 6 AEs of asthenia in 6 (3.4 %) subjects were reported. Apart from these AEs, small group of subjects reported cough, headache, myalgia, malaise, and many other non-significant AEs were reported. Out of the 90 AEs reported only 6 AEs were of moderate intensity. All observed effects were transient. And no actions were required against the reported AEs. No serious adverse events were reported during the study. All the AEs were completely resolved. The GMT values of SARS-CoV-2 Glycoprotein specific Antibodies (29045.97) and VNA (242.32) on day 42 were non-inferior and numerically greater than data from Russia Phase I/II and Phase III investigations (1648.42 and 16.28).

Considering the emergence of Omicron strain in India and to assess the activity of Sputnik light vaccine against Omicron variant (B.1.1.529); Day 28 serum samples of randomly selected subjects (N=30) who were vaccinated with Sputnik light vector vaccine as part of the study were tested for virus neutralizing activity (VNA) against Omicron strain at Bioassay Laboratory, THSTI. Ninety-three percent (93%) of the subjects (28 out of 30) demonstrated virus neutralizing activity against the Omicron strain. This suggests that Sputnik light vaccine is active against Omicron variant as well.

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