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Evaluating the efficacy and safety of a novel prophylactic nasal spray in the prevention of SARS-CoV-2 infection: A multi-centre, double blind, placebo-controlled, randomised trial.

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ABSTRACT

Background The COVID-19 pandemic continues to devastate communities all over the world. The aim of this study was to evaluate the efficacy and safety of the test agent as a prophylaxis against SARS-CoV-2 infection in a population of high-risk healthcare workers.

Methods The study was a multi-centre, prospective, double blind, randomized, placebo-controlled trial. Key eligibility criteria included absence of significant co-morbidity and no previous SARS-CoV-2 infection or vaccination. Participants were randomised to either the active agent nasal spray or placebo using computer generated random number tables. The nasal spray was administered 3 times daily over a 45 day course. The primary end point was the percentage of subjects who tested positive for IgGS (anti-spike, immunoglobulin G specific to the spike protein of SARS-CoV-2) at day 45.

Results Between 16th April 2021 and 26th July 2021, 556 participants were analysed for the primary endpoint (275 Test; 281 Placebo). The test agent significantly reduced SARS-CoV-2 infection compared to placebo [36 cases (13.1%) Vs 97 cases (34.5%); OR 0.29 (95% CI; 0.18–0.45), $p < 0.0001$]. Fewer clinical symptoms were also seen in the test group [57 cases (17.6%) vs 112 cases (34.6%); OR 0.40, (95% CI; 0.27–0.59), $p < 0.0001$]. No harmful effects were associated with taking the test agent.

Conclusion The test agent significantly reduced SARS-CoV-2 infection in healthcare workers, with 62% fewer infections when compared to placebo. It was found to be safe and well tolerated and offers a novel treatment option for prophylaxis against SARS-CoV-2 infection.

1. Introduction

Rapid advances have been made in vaccination against SARS-CoV-2 and in the treatment of COVID-19. However, the virus continues to infect and kill people all over the world [1]. Many low-income countries have difficulty obtaining vaccines or affording the more expensive

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therapies and globally there is a significant issue with vaccine hesitancy. Given the importance globally of the SARS-CoV-2 pandemic, multiple approaches to prevent and treat infections need to be found. One approach would be to block viral ingress at the time of infection, significantly lowering viral load and potentially preventing infection, replication and transmission.

Recent work around the COVID-19 pandemic has focused on providing a deeper understanding of the human-to-human modes of transmission of SARS-CoV-2 [2,3] and its mechanism of entry in host cells [4], highlighting the need for preventive interventions. To date, researchers have demonstrated that SARS-CoV-2 can enter host cells via an acidic pH-dependant pathway [5–7]. Facilitation of SARS-CoV-2 entry into host cells is mediated through a structural protein, the spike (S) protein, which interacts with the Angiotensin-Converting Enzyme 2 (ACE-2) receptors present on the surface of these host cells [7]. In addition to ACE-2 receptors, key target-cell proteases such as furin [8–10], TMPRSS2 [5,11] and cathepsin L [12,13] are utilized by the virus and studies have provided further insight into the SARS-CoV-2 entry pathway. This study reports the development of a prophylactic nasal spray targeted to the SARS-CoV-2 virus that is simple to produce and easily affordable.

The test formulation combines natural virucidal agents with a patented system designed to alter the optimal acidic environment required for cell invasion, hence preventing viral entry into the nasal epithelium. In vitro, the mechanism of action is such that the natural virucides reduced the levels of the SARS-CoV-2 from 4.5 to <1.7 $\log_{10}$ $CCID_{50}$ per 0.1 mL, which is equivalent to a 99% reduction in virus titer. In addition, the test agent reduces acidification of endosomes and the SARS-CoV-2 S1/ACE2 interaction, and inhibits Cathepsin L and Furin, host proteases which promote proteolytic activation of viral proteins. Together, these combined actions work to reduce the initial viral load exposure.

Extensive preclinical in vitro and in vivo experiments have established that the test agent is stable when stored for more than 12 months at room temperature and is well tolerated. In vivo pre-clinical studies revealed no signs of mucosal membrane irritation while in vivo pre-clinical safety studies in both mouse and rabbit models demonstrated no evidence of toxicity upon intranasal administration of our test agent thrice daily for 28 consecutive days. A separate manuscript detailing the test agent's in vitro mechanism and in vivo activity is currently being prepared.

All the components in the test agent were deliberately selected to be inexpensive, stable, readily available globally and, most importantly, already described in Pharmacopeia or equivalent documents in several countries world-wide.

The objective of this study is to assess the efficacy and safety of the test agent in acting as a prophylaxis against SARS-CoV-2 infection in a population of high-risk healthcare workers in India.

2. Methods

2.1. Composition of the test agent

The test agent was developed by Raphael Labs Ltd (London, United Kingdom) and formulated in collaboration with Dabur Research Foundation (Uttar Pradesh, India).

The components of the test spray include sterile water, polyethylene glycol 400, poloxamer 188, xylitol, disodium hydrogen phosphate, sodium chloride, hydroxypropyl methylcellulose, ginger oil, eucalyptus oil, basil oil, clove oil, sodium hydrogen carbonate, potassium dihydrogen phosphate, ethylenediaminetetraacetic acid, sodium hyaluronate, calcium chloride dihydrate, benzalkonium chloride, magnesium chloride hexahydrate, potassium chloride, glycerol, and zinc chloride.

2.2. Trial design

The study was a multi-centre, prospective, double blind, randomized (1:1) placebo-controlled trial to assess the efficacy and safety of the test agent spray in the prevention of SARS-CoV-2 infection in high-risk healthcare professionals over 45 days of treatment.

2.3. Participants

Participants were recruited from populations of healthcare workers from two Indian hospitals (Tulsi Hospital, Kanpur, Uttar Pradesh; and Atharva Multispeciality Hospital, Lucknow, Uttar Pradesh) between April and July 2021, during the peak surge of the Delta (B.1.617.2) variant in India. Healthcare workers were studied due to their high exposure to SARS-CoV-2 infection. Participants were frontline workers from across all hospital departments including doctors, nurses, physiotherapists and pharmicists as well as administrative staff such as hospital executives, receptionists, and cleaners. Inclusion criteria were, age greater than 18 years and the absence of significant comorbidities. Exclusion criteria included pregnancy or lactation, recipients of blood products or immunoglobulin within the last 3 months or during the study period, participation in other clinical trials in the last 3 months, drug or alcohol abuse, previous vaccination against SARS-CoV-2 infection, participation in other SARS-CoV-2 trials, or evidence of previous SARS-CoV-2 (positive serum IgGS, Reverse transcription – polymerase chain reaction (rt-PCR) and medical history). Participants also agreed not to take any over the counter products throughout the study duration.

2.4. Randomisation and masking

Participants were randomly assigned to either the test agent nasal spray or placebo groups using computer generated random number tables (SPSS version 20.0). Allocation concealment was ensured using an external unblinded pharmacist for repackaging both sprays in identical packaging.

2.5. Procedures

Subjects were randomised to either the test agent nasal spray, or a placebo. Nasal spray was administered up to three times per day (TID) 140 μl/nostril for 45 days, with a gap of 6–8 h between doses. Regimen compliance was assessed by measuring used versus unused nasal spray volumes, and a compliance rate of less than 80% of required doses was classified as a protocol violation. In-person assessment including physical examination, assessment of vital signs and assessment of symptoms/adverse reactions was performed at days 16, 32, and 45 with interim telephone assessments performed at days 8, 24, and 40. Serum IgGS (anti-spike, immunoglobulin G specific to the spike protein of SARS-CoV-2) was measured on day 1 and day 45 (SARS-CoV-2 IgG Assay, Seimans Healthineers, Germany). Standard haematology and biochemistry blood tests were measured at day 1 and day 60. User acceptability was assessed on days 16 and 45.

2.6. Outcomes

The primary endpoint was IgGS seroconversion at day 45. These antibodies have been shown to be elevated in serum for several weeks after diagnosis of COVID-19 [14,15].

Secondary endpoints measured included:

- Development of clinical symptoms of SARS-CoV-2 over the 45 days of treatment: These were defined as fever, cough, shortness of breath, sore throat, abdominal pain, fatigue, rhinorrhoea, nausea and vomiting, diarrhoea, rash, conjunctivitis, muscle ache, joint ache, loss of appetite, epistaxis, and impaired sense of taste and smell [16].

- Acceptability of the treatments: Assessed in terms of comfort, ease of carriage, ease of use, odour, and overall experience.
- Safety assessment via recording and reporting of all adverse reactions to the product.

2.7. Changes to methods after trial commencement

The initial primary endpoint was the percentage of subjects who tested positive for SARS-CoV-2 on reverse-transcription Polymerase Chain Reaction (rt-PCR). An issue was detected in the analysis of rt-PCR during the study and the positivity rate at the lab dropped from 15% to below 0.5%, well below the national average for India at that point. With the go-ahead from the regulator and ethics boards positive serum immunoglobulin G specific to the spike protein of SARS-CoV-2 (IgGS) was substituted as the primary endpoint.

2.8. Statistical analysis

The sample size calculation was based on a clinical superiority design, assuming the superiority margin of ability to detect a clinically relevant difference in the primary outcome of 50% between the two trial arms. Anticipated rate of event was 10% for the test agent group and 50% for the control group. To achieve a 90% power at a two-sided 5% significance level with equal (1:1) allocation and a 10% dropout rate, the sample size calculation indicated that 324 participants would be required in both groups giving a combined sample size of 648 participants.

Between-group comparisons were performed using Fisher's exact test and Chi-squared test for categorical data and Mann-Whitney U test for continuous data. Multi-variate analysis for the primary endpoint was performed using binary logistical regression with baseline demographic data and treatment group as covariables. All statistical tests were 2-sided and performed at the 5% level of significance using SPSS Version 20.0.

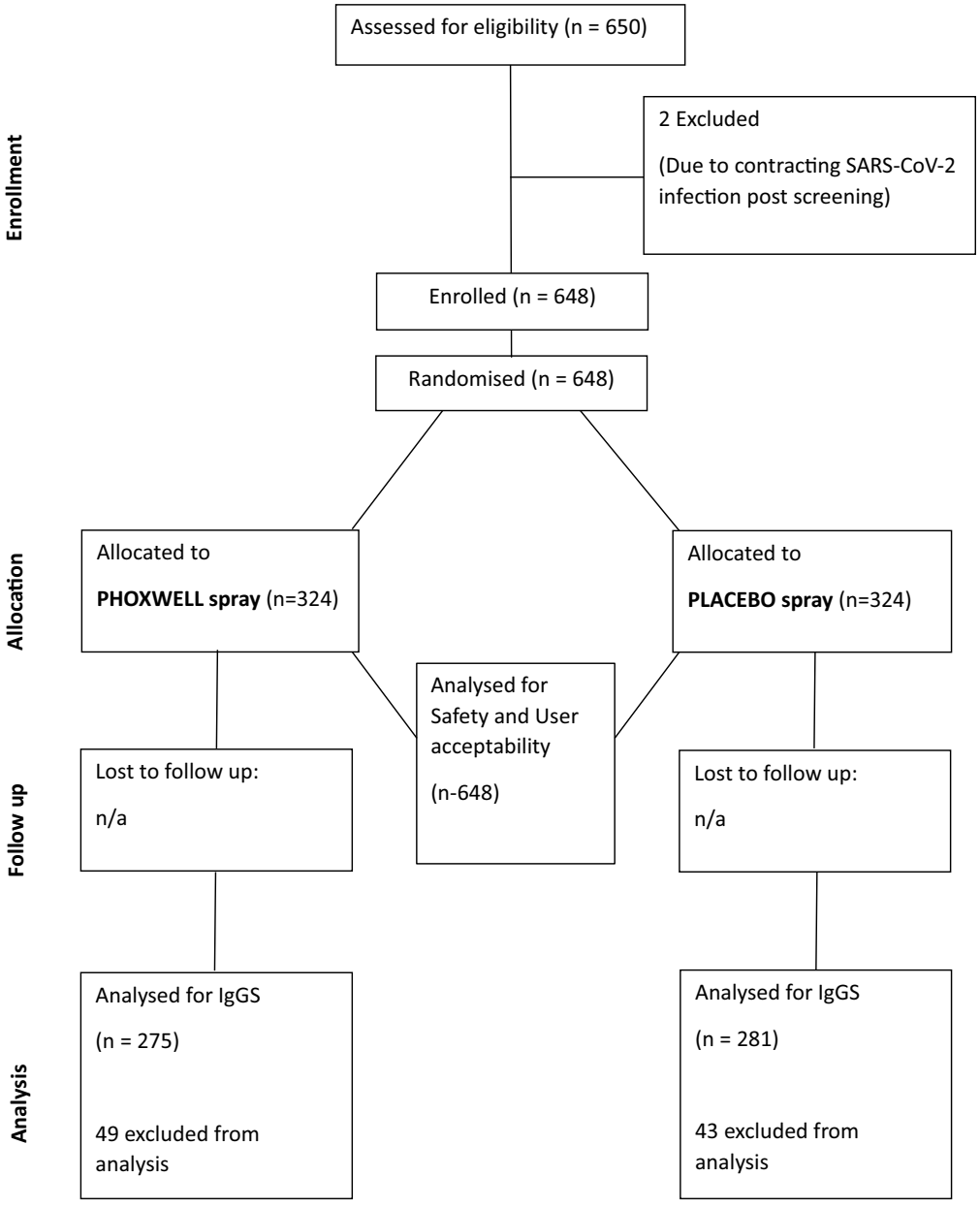

Fig. 1. Participant flow diagram for the trial.

2.9. Ethics

The Institutional Ethics Committees (IEC) for both Atharva Multi-specialty Hospital and Research Centre (Ref:NIEC/INDT/APP/17/04/21/01) and Tulsi Hospital (Ref: THEC/CT/003/2021) approved the study. The trial was registered prospectively with The Clinical Trials Registry – India (CTRI) trial registration number: CTRI/2021/04/032,989.

3. Results

Between 16th April 2021 and 26th July 2021, 650 subjects were screened with 648 being randomised. All randomized subjects were included in the safety and acceptability analysis sets. 92 (14.2%) of the randomized subjects were excluded from the analysis of the primary endpoint as they were enroled prior to the change in primary endpoint to IgGS serology. (Fig. 1). 49 (15.1%) were excluded from the test agent group and 43 (13.3%) from the placebo group.

Baseline demographics for the two treatment groups are given in Table 1. Mean age was statistically different between the two groups at 43.3 years in the test group compared to 40.3 years in the placebo ($p = 0.0255$).

556 participants (85.8%) who underwent IgGS testing were included in the primary endpoint analysis. On univariate analysis, a statistically significant reduction in the development of IgGS positive SARS-CoV-2 infection was seen in the test agent cohort compared to placebo [36 cases (13.1%) Vs 97 cases (34.5%); OR 0.29 (95% CI; 0.18–0.45), $p < 0.0001$] (Table 2). This represents a 62% relative risk reduction in infection rate.

This result was consistent across sites (Atharva Hospital 17.4% vs 54.6% $p < 0.0001$; Tulsi Hospital 11.1% vs 23.9%, $p = 0.0015$), sex (male 13.6% vs 36.6% $p < 0.0001$; 12.1% vs 31.2% $p = 0.0013$) and age groups (18–35 14.7% vs 28.6% $p = 0.0122$; 35–65 12.5% vs 40.8% $p < 0.0001$; 65+ 10.3% vs 33.3% $p = 0.0676$). Table 2 summarises this data.

On multivariate analysis, 'treatment group' was an independent predictor of IgGS seroconversion with the test agent spray demonstrating a protective effect (OR 0.28; $p < 0.0001$) (table 3). Working at the Atharva Hospital rather than Tulsi Hospital (OR 3.02; $p < 0.0001$) was also a significant independent predictor of IgGS seroconversion. Age was not found to be associated with the development of IgGS seroconversion. This negates any potential effect of the difference in ages between the two treatment groups that occurred by chance in the randomisation process.

A statistically significant reduction in experiencing any clinical symptom was seen in those treated with the test agent compared to placebo [57 cases (17.6%) vs 112 cases (34.6%); OR 0.40, (95% CI; 0.27–0.59), $p < 0.0001$]. As per the primary endpoint, these results were reflected across sex (male 15.3% vs 31.8% $p = 0.0001$; female 21.7% vs 39% $p = 0.0048$) and all age groups (18–35; 26.5% vs 43.6% $p = 0.009$: 36–65; 19.4% vs 36.9% $p = 0.0018$: 65+; 6.9% vs 33/3% $p = 0.0407$). A breakdown of all symptoms experienced in either treatment arm is given in Appendix 2; Supplementary information.

Mean time to resolution of symptoms was 1.74 days in the test agent

Table 1
Demographic characteristics.

Characteristic	Result	Test agent spray ($n = 275$)	Placebo spray ($n = 281$)	p-value
Age (years)	N	275	281	
Mean (+/- SD)	Mean	43.3 +/- 16.3	40.3+/- 14.9	0.0255
	Standard Deviation	16.3	14.9	
	Minimum	18	18	
	Median	43	36	
	Maximum	91	84	
BMI (kg/m2)	N	275	281	
	Mean	23.7 (+/−2.4)	23.9	0.3969
	Standard Deviation	2.4	2.7	
	Minimum	13.6	17.7	
	Median	24	23.9	
	Maximum	30.1	33.8	
Gender (n,%)	Male	176 (64%)	172 (61.2%)	0.5397
	Female	99 (36%)	109 (38.8%)	
Study site (n, %)	Tulsi Hospital	189 (68.7%)	184 (65.5%)	0.4185
	Atharv Multi. Hospital	86 (31.3%)	97 (34.5%)	

Table 2
Comparison of serum IgGS positive between the treatment groups.

	Test agent spray ($n = 275$)	Placebo spray ($n = 281$)	OR(95% CI)	p-value
Total Cohort	36 (13.1%)	97 (34.5%)	0.29 (0.18–0.45)	$P <$ 0.0001
Sites	15 (17.4%)	53 (54.6%)		
Atharva Hospital	21 (11.1%)	44 (23.9%)	0.18 (0.08–0.36)	$P <$ 0.0001
Tulsi Hospital			0.40 (0.21–0.72)	$p =$ 0.0013
Gender	24 (13.6%)	63 (36.6%)		
Male	12 (12.1%)	34 (31.2%)	0.27 (0.15–0.48)	$P <$ 0.0001
Female			0.31 (0.13–0.66)	$p =$ 0.0013
Age	15 (14.7%)	38 (28.6%)		
18–35	18 (12.5%)	53 (40.8%)	0.43 (0.21–0.87)	$p =$ 0.0122
36–65	3 (10.3%)	6 (33.3%)	0.21 (0.11–0.39)	$p <$ 0.0001
65+			0.24 (0.03–1.34)	$p <$ 0.0676

Table 3
Multivariate logistic regression of IgG positivity rate.

Covariates	Odds ratio	95% CI	p-value
Treatment (reference: Placebo spray)	0.28	(0.18, 0.43)	<0.0001
Age	1.00	(0.99, 1.02)	0.8515
Gender (reference: Female)	1.12	(0.72, 1.75)	0.6001
BMI	1.07	(0.98, 1.16)	0.1322
Study site (reference: Tulsi Hospital)	3.02	(1.97, 4.63)	<0.0001

Table 4
Comparison of development of any clinical symptoms between the treatment groups.

	Test agent spray($n = 275$)	Placebo spray($n = 281$)	OR(95% CI)	p-value
Any symptoms (Total Cohort)	57 (17.6%)	112 (34.6%)	0.40, (0.27, 0.59)	$P <$ 0.0001
Gender	32 (15.3%)	64 (31.8%)		
Male	25 (21.7%)	48 (39.0%)	0.39 (0.23–0.640	$p =$ 0.0001
Female			0.44 (0.23–0.80)	$p =$ 0.0048
Age	27 (26.5%)	58 (43.6%)		
18–35	28 (19.4%)	48 (36.9%)	0.47 (0.25–0.84)	$p =$ 0.0091
36–65	2 (6.9%)	6 (33.3%)	0.41 (0.23–0.73)	$p =$ 0.0018
65+			0.15 (0.01–1.03)	$p =$ 0.004
Days to resolution of clinical symptoms (mean/SD).	1.74 (0.83)	1.95 (1.05)		$p =$ 0.1729

group compared to 1.95 days for the placebo ($p = 0.1729$) (Table 4). A comparison of SARS-CoV-2 IgGS antibody status and symptom status for each treatment group is shown in Table 5. This analysis shows that for participants who did not contract SARS-CoV-2 infection during the study period as evidenced by a negative IgGS antibody result, reported symptoms were significantly lower in the test agent group [$n = 35$ (14.5%)] than in the placebo group [$n = 67$ (36.4%)] ($p < 0.001$). No significant difference was seen in the proportion of patients who reported symptoms amongst patients who tested positive for IgGS.

Acceptability testing showed that subjects had a positive experience of using both the test agent and placebo nasal sprays (Fig. 2). Both sprays were comfortable to use, easy to carry, easy to use and had an acceptable odour (Appendix 1: supplementary information). No serious adverse events (SAEs) were reported and no subjects died. No significant differences were seen on physical examination, haematology or biochemistry (Appendix 2; supplemental information). Greater than 80% compliance with required doses was achieved in 99.4% of patients with just 3 patients in the test agent group and 1 patient in the placebo group falling below the compliance standard.

4. Discussion

The test agent has been shown to significantly reduce SARS-CoV-2 infections in high-risk healthcare workers, with 62% fewer infections compared to placebo (13.1% vs 34.5%; $p < 0.0001$). Whilst participants working at the Atharva Hospital were found to be more at risk of IgGS seroconversion than those working at the Tulsi Hospital, a significant protective effect of the test agent nasal spray was seen at both sites. (Table 2). The infection rate in the Atharva Hospital was expected to be higher as it was a government dedicated covid treatment hospital with a significantly higher foot fall than the Tulsi Hospital, a private institution with covid treatment facilities.

The benefits of the test agent spray were further supported by a significant reduction in symptoms when compared to placebo (17.6% vs 34.6% $p < 0.0001$), This study also demonstrated that the test agent was well tolerated, with good user acceptability and a benign safety profile.

To date, several in-vitro and animal studies have investigated the use of nasal spray formulations in the post-exposure prophylaxis of SARS-CoV-19 infection [17–19]. A wide range of substances aimed at blocking viral entry to the host have been proposed for nasal administration and are currently being trialled in humans including quinine, nitric oxide, and povidine iodine [20]. To our knowledge only one previous study reports on the outcomes of nasal sprays in the prophylaxis of SARS-CoV-19. Figueroa et al., performed a randomised, placebo controlled trial in 394 patients of a nasal spray containing Iota-Carrageenan and found a significant reduction in infection rate from 5% in the control group down to 1% [21]. This study was limited in that only patients who developed symptoms of COVID-19 infection were tested. Therefore, the rate of asymptomatic infection in either arm of the study was not known. More recently, nasal administered monoclonal antibodies have been developed and have proven effective in reducing SARS-CoV-2 infection in animal models [22]. No previous studies have been conducted using this test agent, so the significant results seen are the baseline for its level of efficacy.

Table 5
Summary of symptomatic vs asymptomatic among IgG positive and negative subjects.

Examination	Test agent spray		Placebo spray	
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
IgG Antibody Positive	11 (30.6%)	25 (69.4%)	39 (40.2%)	58 (59.8%)
Between-group comparison: Odds ratio = 0.66, 95% CI = (0.26, 1.58), P-value = 0.4205				
IgG Antibody Negative	35 (14.6%)	204 (85.4%)	67 (36.4%)	117 (63.6%)

Between-group comparison: Odds ratio = 0.30, 95% CI = (0.18, 0.49), P-value < 0.0001.

The strengths of the current study are that it is a well-designed multicentre-double blinded randomised controlled trial. It was also adequately powered to show a strong positive efficacy signal for the test agent. Due to the fact that all study participants were tested for SARS-CoV-2 infection, both symptomatic and asymptomatic infection was detected. The study was conducted during the delta variant surge in India meaning that exposure rates to a highly infective variant would have been high. This is supported by the fact that infection rates in the placebo group were high with 34.5% of subjects testing positive for IgGS in the 45 day study period.

A limitation of the study is that an issue with the rt-PCR processing at the central lab resulted in the primary endpoint being changed to IgGS serology. This change reduced the number of subjects available for analysis for the primary endpoint from 648 to 556 but despite this the reduction in SARS-CoV-2 infection in the test group remained highly significant.

The test agent's high prophylactic efficacy could have a significant effect on the disease burden of SARS-CoV-2 and COVID-19. Its low cost and ease of storage could make it a valuable resource in lower income countries where vaccination rates are low. Given its mechanism of action, the test agent is designed to act in parallel and synergistically to vaccination, PPE (including masque wearing) and social measures as a further level of protection against SARS-CoV-2. It could also benefit those who are vaccine hesitant, immunosuppressed or in those opposed to vaccination entirely. In the future, a larger prophylaxis study in a wider population is required to validate and strengthen these initial results.

With the emergence of different variants of the SARS-CoV-2 virus there is uncertainty over the ongoing efficacy of vaccination. Since the targeted mode of SARS-CoV-2 entry into the cells is shared by the more recent Omicron variant, we anticipate that the test agent will be remain equally effective against this and future SARS-CoV-2 variants, although confirmatory studies would be required.

There is also the potential for the test agent to be active against other viruses with similar mechanisms of entry, such as influenza and the current study provides some evidence for this. In participants with negative IgGS, its use significantly reduced the proportion reporting symptoms of infection (Table 5). There are two possible explanations for these results. The first is that the test agent spray is preventing infection by other respiratory viruses with a similar mechanism of entry. A second explanation is that it is acting therapeutically and preventing subjects from developing symptoms of infection even if they have contracted a similar virus. Clinical studies into prophylaxis against Influenza and other viruses should be undertaken to further evaluate this finding.

5. Conclusions

SARS-CoV-2 continues to pose a significant public health emergency globally. In the current study, the test agent nasal spray has been shown to significantly reduce SARS-CoV-2 infections in healthcare workers, with 62% fewer infections when compared to placebo.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

JAS, LS, AD, KED, SGD, MAM, AM, RM, DR, AJR, and RU are

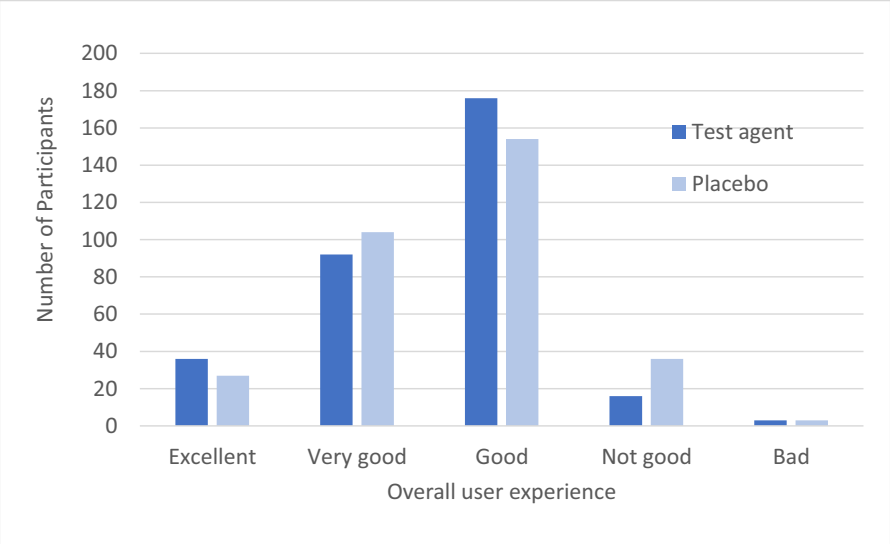

Fig. 2. Comparison of overall user experience between the test agent and placebo treatment groups.

shareholders of Raphael Labs LTD. JS is the managing director of Swales Pharma Consulting providing consulting services for a range of pharmaceutical companies. AJM and AR sit on the advisory board of Raphael labs.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2022.105248.

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