Brief protocol title	T2R-002
Formal protocol title	Efficacy, Safety, and Tolerability of GLS-1200 Topical Nasal Spray in the Prevention of Incident Confirmed SARS-CoV-2 Infection
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Version Summary

Initial version:	Version 7.0	26 February 2021
Amendment:		

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PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and receive approval or a favorable opinion before implementation.

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

Investigator's printed name and signature	Date
	26 February 2021
Medical Monitor	Date

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CLINICAL PROTOCOL SYNOPSIS

Title of study: Efficacy, Safety, and Tolerability of GLS-1200 Topical Nasal Spray in the Prevention of Incident Confirmed SARS-CoV-2 Infection

Number of study sites and Countries/Regions: 2, US

Target Number of study participants: 225

Study Phase: II

Study Type: Randomized, placebo-controlled, double-blind

Research Hypothesis: GLS-1200 topical nasal spray will be well tolerated and can reduce the incidence of confirmed SARS-CoV-2 infection

Primary study objectives and outcome variables:

- Evaluate the safety and tolerability of GLS-1200 topical nasal spray
- Incidence of SARS-CoV-2 infection, confirmed by PCR relative to treatment group

Secondary study objectives and outcome variables:

- Documentation of symptoms consistent with SARS-CoV-2 infections relative to treatment group

Exploratory study objectives and outcome variables:

- Incidence of SARS-CoV-2 seroconversion relative to treatment group
- Assess the relationship of taste receptor genetics to incidence of SARS-CoV-2 infection and relative to treatment group

Table S1: Dosing arms and treatment regimen

Group	N	Treatment assignment	Study drug	Diluent	Spray volume	Treatment schedule
1	150	GLS-1200	1 mg/mL quinine sulfate, dihydrate	0.9% sterile saline	1 mL/ nostril	TID x 4 weeks
2	75	Placebo (0.9% sterile saline)	0.9% sodium chloride solution	N/A	1 mL/ nostril	TID x 4 weeks

Study design: This Phase II randomized, placebo-controlled, double-blind study will assess whether topical GLS-1200 applied via nasal spray atomizer is well-tolerated and can reduce the incidence of confirmed SARS-CoV-2 infection. Subjects will be randomized to either GLS-1200 or placebo group in a 2:1 ratio with a target enrollment of 225 subjects. Subjects will self-administer study drug three times daily (TID) for 4 weeks.

Safety assessments: Participants will be monitored for adverse events. Laboratory and electrocardiographic (ECG) safety assessments will be performed at baseline and at the completion of 4 weeks of treatment. Subjects will complete a diary with daily entries to document clinical symptoms consistent with SARS-CoV-2 infection.

Study population:

Inclusion criteria:

1. Age 18 years or older
2. Able to provide informed consent
3. Able and willing to comply with study procedures
4. Able and willing to utilize an approved form of pregnancy prevention for women of child-bearing potential through to the end of treatment.

Exclusion criteria:

1. Known allergy to quinine or quinidine or mefloquine
2. Confirmed prior positive test for SARS-CoV-2

3. Treatment within the past 2 weeks with chloroquine, hydroxychloroquine, or remdesivir
4. Pregnancy or documentation of pregnancy by pre-treatment urine pregnancy test or breast feeding or plans to become pregnant during the course of the study

Table S2: Schedule of Events

Tests and Observations	**Day 0**	**Week 2**	**Week 4**	**Week 6**	**Unscheduled**
Permitted window (days)		±3d	±3d	±3d	N/A
Clinical Evaluations					
Obtain Written Informed Consent	X				
Confirm Eligibility Criteria	X				
Demographics	X				
Medical History and Concomitant Medications	X	X	X	X	
Physical Exam, height, weight, and Vital Signs[1]	X	X	X	X	X
Safety Evaluations					
Record Adverse Events		X	X	X	X
Provide participant diary	X				
Collect and review participant diary		X[2]	X	X	
Perform 12-lead ECG	X		X		
Pregnancy test[3]	X	X	X		
Blood for Hematology: CBC with differential	X		X		
Blood for Chemistry: Sodium, potassium, bicarbonate, glucose, BUN, Cr	X		X		
Study Related Procedures					
Dispense study drug & device, provide training	X				
Collect nasopharyngeal swabs for viral PCR	X	X	X	X	X
Collect serum for viral antibodies	X	X	X	X	
Collect plasma for measurement of quinine		X			
Collect saliva for TAS2R genotyping	X				
Estimated Blood Volume per Visit (mL)	40	25	40	20	

[1] A targeted physical exam will be performed at Weeks 2, 4 and 6 and at unscheduled visits.
[2] The participant diary will only be reviewed at Weeks 2 and 4; it will be reviewed and collected at Week 6.
[3] A urine pregnancy test will be administered.

1. INTRODUCTION

This study will examine whether GLS-1200 topical nasal spray is safe, well tolerated and can reduce the risk of incident infection from SARS-CoV-2 as confirmed by PCR. GLS-1200 is a formulation of quinine sulfate, dihydrate at 1 mg/mL in 0.9% saline.

1.1 Background and Rationale

Quinine is a known agonist for multiple bitter taste receptors (TAS2Rs). TAS2Rs not only line the tongue, but are also expressed on the surface of ciliated nasal epithelial cells. These TAS2Rs are a component of the innate immune system and the functionality of specific TAS2Rs is genetically determined with almost equal prevalence of functional and non-functional genotypes in the population. Quinine stimulation of ciliated nasal epithelial cells induces release of nitric oxide (NO). Release of NO from epithelial cells has been shown to reduce the growth of pathogenic bacteria. NO is also able to inhibit viral replication of numerous viruses including the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). Since the nares are a likely primary portal of entry for the SARS-CoV-2 virus, a virus highly related to SARS-CoV, it is postulated that SARS-CoV-2 infection via the nasal route may be suppressed by quinine-induced NO production from ciliated nasal epithelial cells, akin to NO suppression of SARS-CoV. Such viral suppression may then be protective and limit the incidence and severity of SARS-CoV-2 infection.

Similarly, improvement of the innate immune response to prevent infection within the nasal cavity has potential to reduce the burden of chronic rhinosinusitis (CRS). It has been shown that stimulation of nasal epithelial cells with phenylthiocarbamate (PTC), another bitter taste receptor agonist, induces transmembrane calcium fluxes that correlate with NO release [1]. This stimulation is associated with reductions in bacterial growth when nasal epithelial cells are overlaid with *Pseudomonas aeruginosa* [1].

Exposure to NO has been shown to inhibit replication for many DNA and RNA viruses including hantavirus [2] and the murine hepatitis coronavirus [3]. Inhaled NO has also been reported to improve human hantavirus infection in a single case report [4].

With regard to whether NO may be helpful in the treatment of SARS-CoV-2 infection, two groups showed that SARS-CoV replication is inhibited by NO as supplied by the NO donor molecule S-nitroso-N-acetylpenicillamine [5] [6]. NO also prevented maturation of the viral S protein through inhibition of palmitoylation that results in reduced binding and viral fusion such that virions have reduced capacity for viral entry into target cells [7].

In humans, bitter and sweet taste perception is governed by G-protein coupled receptors originally identified in oral taste bud type II cells [8] [9]. Receptors belonging to Taste Receptor Family-1 subtypes 2 and 3 (T1R2/T1R3) detect sweet compounds such as glucose and sucrose. Greater than 50 Taste Receptor Family-2 (T2Rs) have been characterized. T2Rs are primarily bitter taste receptors and respond to a variety of bitter compounds including caffeine, denatonium, strychnine and quinine [10]. One subset of T2Rs, when activated, stimulates the respiratory epithelium to generate NO, while a second subset of T2Rs expressed on solitary chemosensory cells (SCCs), can stimulate release of antimicrobial peptides. Both T2R-mediated pathways are considered integral to the upper airway innate immune defense system [1] [11] [12].

Stimulation of T2Rs activates the canonical taste signaling cascade involving phospholipase C β2 (PLCβ2) and transient receptor potential cation channel subfamily M member 5 [1]. More recently, bitter and sweet receptors have been discovered in a variety of extra-oral tissues including the brain, thyroid, pancreas, testes and throughout the respiratory and gastrointestinal tracts [13] [14] [15].

In the airway, taste receptors are present on a variety of cell types and have been shown to mediate several complementary components of innate immune defense. For example, ciliated sinonasal epithelial cells express T2R38 and respond to PTC and acyl-homoserine lactones, bitter compounds released by gram-negative bacteria such as *Pseudomonas aeruginosa*. Activation of T2R38 triggers an increase in intracellular calcium (Ca^{2+}) yielding stimulation of NO synthase with resultant production of intracellular NO [16]. The NO, through cyclic GMP, increases ciliary beat frequency (CBF) and diffuses into the mucus layer where it has direct bactericidal activity [16] [17] [18]. Similarly, SCCs, rare epithelial cells that express both T1R2/3 and T2R receptors [19], also respond to bitter compounds secreted by bacteria in the upper airway. Stimulation of T2Rs on the surface of human SCCs by the bitter agonist denatonium elicits a calcium response that spreads via gap junctions to neighboring epithelial cells, triggering a release of pre-formed stores of antimicrobial peptides [1] [20]. At the present time, it is thought that the repertoire of T2Rs expressed on ciliated cells and the repertoire of T2Rs expressed on SCCs are mutually exclusive. Recent work demonstrates that the NO-producing T2R response is exclusively found in ciliated cells, while production of antimicrobial peptides is driven only by T2R's on SCCs [16] [1] [21].

The genes encoding the *TAS2Rs* localize primarily to chromosomes 7 and 12, each with functional and non-functional polymorphisms [22] [23]. The correlation between taste receptor genetics and function and its potential role in sinusitis presentation and outcome was first characterized for the bitter taste receptor T2R38. The gene for this bitter receptor, TAS2R38, has two prevalent allele polymorphisms that correlate with taste receptor function. Functional alleles are characterized by a position 49 proline, position 262 alanine, and position 296 valine (known as a PAV genotype) versus alanine, valine, and isoleucine at the respective positions (AVI genotype) for the non-functional allele [11]. Individuals who possess two functional alleles are considered as super tasters who are able to perceive bitter compounds such as propylthiouracil. Those with two AVI alleles are considered non-tasters and those with a single allele have heterogeneous taste perception [11] [24]. Importantly, TAS2R38 allelic makeup directly correlates with ability to generate NO in response to TAS2R38 stimulation and clear *Ps. aeruginosa* of explanted sinonasal ciliated cells [16].

Genetic variations in taste receptor functionality cause differential responsiveness in cells isolated from different individuals, and corresponding taste receptor function correlates with disease severity in CRS [1] [16] [25] [26] [27]. This has been best characterized for patients who are homozygous for the non-functional variant of T2R38. They are more likely to require surgical intervention for CRS, and more likely to develop a Gram-negative infection. Recent work has shown that phenotypic taste tests with denatonium, a broad T2R agonist, and sucrose, a T1R2/3 agonist, can reflect clinical disease status in CRS and partially stratify control subjects and CRS patients [28]. It is thought that patients with CRS possess hypo-responsive bitter taste receptors, rating denatonium as less bitter than controls, while also possessing hypersensitive sweet taste receptors, which compounds the reduced antimicrobial response to sinonasal pathogens.

Quinine is derived from the bark of the cinchona tree. It is a centuries-old treatment for malaria, an ingredient in tonic water, and is also an agonist for multiple bitter taste receptors. Activation of

quinine-responsive bitter taste receptors, as discussed below and reviewed elsewhere [16] [17] [29] [30], stimulates the respiratory epithelium to generate NO that, in turn, increases mucociliary clearance and diffuses into the mucus where it is bactericidal. Quinine stimulates multiple bitter taste receptors including TAS2R4, TAS2R14, TAS2R31, TAS2R40, TAS2R43, and TAS2R46 as well as others. Whether one or more is important in the innate immune response is not known, nor has genetic background been correlated with clinical outcome as yet. A topical therapy to activate these taste receptors may help the sinuses clear infections through this natural innate defense mechanism, especially with a lower bacterial or viral burden.

This study will explore the potential role of topical GLS-1200 to prevent confirmed infection from SARS-CoV-2. Individuals are to be recruited and assigned to either GLS-1200 or placebo treatment in a 2:1 ratio to be self-administered for 4 weeks. The primary outcome measures are the safety and tolerability of GLS-1200 nasal spray use and the incidence of SARS-CoV-2 infection, as confirmed by PCR, relative to treatment group.

1.1.1 Pre-clinical experience with quinine

There is extensive literature regarding the ability of quinine to stimulate bitter taste receptors. In this section, we address the physiologic and functional changes that occur following quinine stimulation and the role that the bitter taste receptors have in innate immunity. The role of the bitter taste receptors is already established in the treatment of acute and chronic rhinosinusitis [31].

Quinine is a bitter agonist and alkaloid derivative isolated from the bark of the cinchona tree. It is known to stimulate nine T2Rs with varying efficacy [32]. Quinine-sensitive T2Rs, including T2R4 [21] and T2R14 [33], are expressed in ciliated epithelial cells. As shown below, quinine stimulates a NO antimicrobial response in the airway, and that individuals in a CRS cohort are less sensitive to quinine in a phenotypic taste test. Additional preliminary work has also demonstrated that quinine stimulation of ciliated nasal epithelial cells appears to reduce viral replication of H1N1 influenza.

1.1.1.1. Quinine stimulation increases NO production in primary human sinonasal cells

NO production was measured in response to quinine stimulation in ciliated sinonasal cells using the fluorescent probe 4-amino-5-methylamino-2',7'-difluorescein (DAF-FM). DAF-FM reacts with NO-derived nitrogen species to form a fluorescent benzotriazole [16]. Using confocal imaging, NO production increases were calculated based on changes in fluorescence intensity. It is important to note that changes in intensity are noted in "DAF-FM units," which can only be utilized in comparison to a control condition or an alternate condition, as absolute DAF-FM unit values may differ between experiments. Successive stimulation of cells with 0.01% and 0.1% quinine in ethanol (arrows) caused a dose-dependent increase in NO production over the course of 15 minutes relative to the ethanol control (Figure 1.1.1.1-1 panel A and panel B, n=6 cultures). Average DAF-FM fluorescence increase was 913.4 ± 125.9 units for quinine-stimulated cultures, compared to a 125.9 ± 6.4 unit increase for cultures stimulated with 0.1% EtOH vehicle (n=3 cultures, $p<0.01$). To demonstrate that increases in DAF-FM were due to the presence of NO and not a different reactive O_2 or nitrogen species, cell cultures were stimulated in the presence of the nitric oxide synthase inhibitor L-N^G-nitroarginine methyl ester (L-NAME). Induction of NO related DAF-FM fluorescence in response to quinine was completely blocked by L-NAME (Figure 1.1.1.1-1 panel C, n=3 cultures).

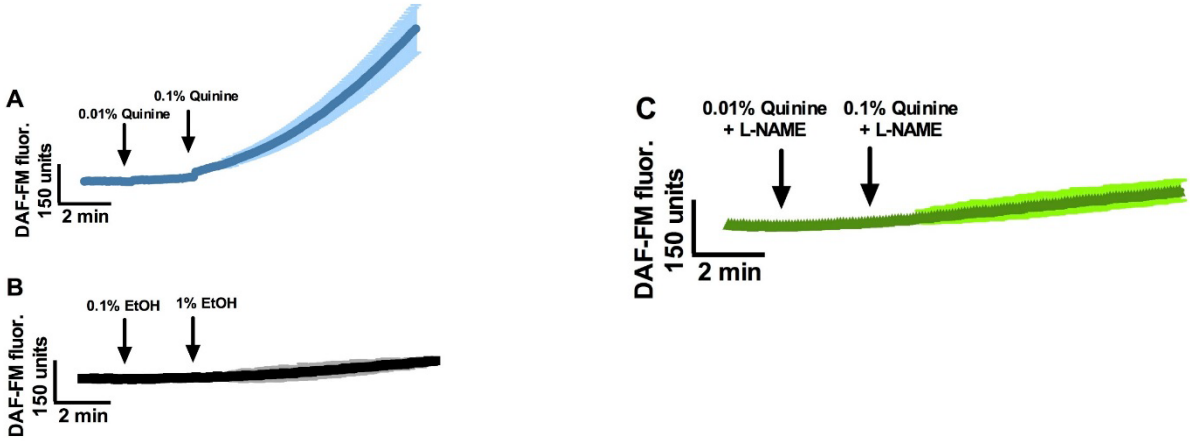

Figure 1.1.1.1-1: Quinine stimulation of NO release in sinonasal cells

1.1.1.2. Quinine stimulation of human ciliated nasal epithelial cells inhibits viral replication of H1N1 influenza A

The ability of quinine to inhibit viral replication was assessed in a human sinonasal air-liquid-interface (ALI) model. ALI derived from two separate patients (A and B) were established. The ALI culture for subject B was more mature and had a higher density of cilia on the apical surface. Both ALI cultures were infected with human H1N1 influenza A strain PR8 at either a multiplicity of infection (MOI) of 1 or 10. One hour post-infection, the cells were stimulated with 0.1% quinine sulfate. The cells were maintained and fed daily for 72 hours with quinine treatment each day. After 72 hours, viral RNA was collected from the cell lysates. PCR of the influenza virus NP, IAV-M1, and M1 genes was performed. As shown in Figure 1.1.1.2-1, there was a marked relative reduction in transcripts for both the NP (panel 1) and IAV-M1 (panel 2) genes in the more mature cells from ALI of subject B and a lesser relative reduction of transcripts in the ALI cells of subject A at a MOI of 1. Both viral RNA and cellular reference gene expression was lower and relative differences were less at the MOI of 10, suggestive of viral destruction of cells. Results for the viral M1 gene were similar (data not shown).

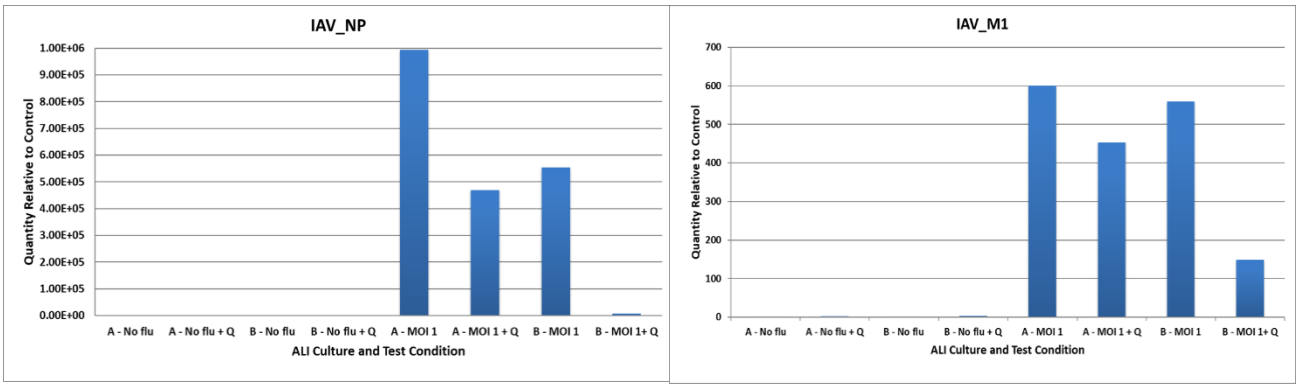

Figure 1.1.1.2-1: PCR transcripts of viral NP and IAV-M1 genes

These data provide evidence of a possible anti-viral effect of quinine via stimulation of NO to inhibit viral replication. This effect may be less with high multiplicity of infection.

1.1.1.4. Relevant studies of other investigators

Several investigations have examined the effect of quinine on the lower airway, particularly in inflammatory modulation and bronchoconstriction. In mouse asthma models, pretreatment of animals with quinine reduces infiltration of inflammatory cells and also attenuates excessive mucus accumulation [34]. Specifically, a dose-dependent reduction of neutrophil and other immune cell recruitment was observed in a chemotactic gradient with quinine administration. Other studies have demonstrated a reduction in bronchoconstriction and airway remodeling with quinine, particularly due to smooth muscle relaxation [35]. The immunomodulatory effects of quinine responsive T2Rs throughout the airway are still being fully elucidated but utilizing quinine as an agonist to stimulate innate immune defenses may have therapeutic potential in CRS and other respiratory diseases.

Common genetic variants in a cluster of bitter taste receptor genes on chromosome 12 appear to have a robust contribution to perception of quinine taste intensity [23]. Quinine taste sensitivity also appears to have been selected independently in some world populations, particularly for low concentrations of quinine [36]. A recent investigation demonstrated that patients with chronic rhinosinusitis with nasal polyps are significantly less sensitive to the bitter taste of quinine. This complements previous data showing that patients with the other CRS phenotype without nasal polyps are significantly less sensitive to denatonium, a broad T2R agonist [28]. However, denatonium is detected by T2Rs located on SCCs, and the SCC downstream response of T2R stimulation is an increase in antimicrobial peptide secretion, while NO release is more characteristic of a ciliated cell T2R response. These two bitter products, denatonium and quinine, elicit different physiologic responses and may each demonstrate unique T2R contributions to the two broad types of CRS (with and without polyps). Previous work also shows that patients with CRS irrespective of phenotype are more sensitive to sucrose, which is a T1R (sweet taste receptor) agonist. As T1R stimulation opposes the action of T2R stimulation in SCCs, these patients are thought to inhibit T2R function at lower airway glucose concentrations, such as during an early airway infection, due to this high affinity. Taste testing that aggregates differences in multiple bitter and sweet taste products that stimulate different receptors may prove useful in achieving improved patient stratification. Further work is necessary to optimize compound concentrations that most accurately reflect taste receptor affinities in the sinonasal tract.

Quinine is a broad T2R agonist that stimulates NO responses with resultant bactericidal activity and increases in mucociliary clearance. The ability of quinine and other bitter tastants to harness innate immune defense mechanisms may have therapeutic potential as topical therapies for sinonasal diseases. Beyond this, inexpensive phenotypic taste tests for quinine and other bitter and sweet compounds can potentially predict airway taste receptor variation and associated predisposition to infectious or inflammatory disorders. Preclinical work has shown both antibacterial and possible antiviral activity.

1.1.2 Human experience with quinine

Quinine has been used in humans for hundreds of years for the treatment of malaria and, more recently, as a treatment for nocturnal leg cramps and other conditions. For the treatment of malaria, a typical oral dose of quinine is 600 mg three times daily and for leg cramps either 200

or 300 mg given at bed time. Quinine is also an additive to tonic water, a form of carbonated water made popular long ago by the British among those living in tropical regions, at a concentration of 83 mg/L – or approximately 30 mg per 8 oz. drink.

There is a large body of experience on the safety and tolerability of quinine given either nasally as a topical irrigation [37] or as an inhaled aerosol [38] [39] [40] [41] [42] [43] (Table 1.1.2-1). The first reported use of quinine delivered nasally was of "1 or 2 grains of quinine [sulphate powder, 65 or 130 mg] … to be fed into the nostrils as one would take tobacco snuff, in cases of facial neuralgia, tic douloureux, and hemicrania" published in the Indian Medical Gazette in 1869 [44]. Quinine has been utilized as a bitter compound to prevent unblinding of participants by masking the taste of the placebo in instances where study drugs were bitter tasting in 7 studies, totaling 652 persons. In these studies, quinine exposures ranged between 2.5 and 90 mg/day (Table 1.1.2-1). The duration of treatment ranged from 14 days to as long as 336 days (48 weeks). While most studies were of outpatients, one studied hospitalized patients admitted with exacerbations of cystic fibrosis (CF) [39]. Quinine exposure in this study was likely 3 mg/day as dosing appears to be the same as the two studies referenced in the methods [41] [43]. Although systemic exposure to quinine was not specifically measured in any study, it is likely that quinine given as inhaled treatment was completely (or near completely) absorbed, whereas quinine given as part of topical nasal irrigation [37] was only fractionally absorbed. Documentation of treatment in some studies was done through qualitative detection of quinine in the urine.

Table 1.1.2-1 Clinical trials utilizing quinine as "placebo" (from published literature)

Disease	Route	# given quinine	Days of quinine	Quinine dose (mg/ml)	# times per day	Vol (ml)	Quinine exposure (mg/day)	Comparator drug	Ref
CRS	Nasal	10	28	1	3	4	12	Tobramycin	[37]
CF	Inh	71	84	1	3	30	90	Tobramycin	[42]
CF	Inh	262	84	0.25	2	5	2.5	Tobramycin	[43]
CF	Inh	9	14	30 µg/kg	2	3.75	~4.2	Glutathione	[38]
CF	Inh	4	14	0.25	4	5	6	Amiloride	[40]
CF	Inh	164	336	0.25	3	4	3	0.9% v 9% saline with quinine	[41]
CF	Inh	132	12.5*	NS	3	4	unk	0.12% v 7% saline with quinine	[39]

CRS, chronic rhinosinusitis. CF, Cystic Fibrosis. NS – not stated; * length of stay was 13 for the 0.12% saline group, 12 for the 7% saline group. * Days of treatment represent an average length of stay through hospitalization as reported.

There were no reported safety issues attributable to quinine usage in the 7 clinical studies. More specifically, there were no reported electrocardiographic or hematologic adverse events reported in the studies. Adverse events documented for comparators such as tinnitus and voice changes for tobramycin [43] were not reported for the "placebo" arms (saline mixed with quinine) of the studies. Thus, quinine appears to be safe at doses similar to or far greater than that used in this protocol and for duration of treatment similar to or longer than proposed for this study.

Quinine also appeared to have a modest effect on CF, there was an early decrease in the density of *Ps. aeruginosa* in expectorated sputum for patients in ***both*** the tobramycin arm and the saline mixed with quinine placebo arm albeit with less of a decrease in the quinine arm of the study [43].

Notably, the difference of *Ps. aeruginosa* colonization density disappeared between the placebo (i.e., quinine) and tobramycin groups at 24 weeks of follow-up. Notably, there was an increase in antibiotic resistance of *Pseudomonas* isolates in the tobramycin arm that was not observed for the placebo (i.e., quinine) arm [43]. A similar effect on colonization of *Ps. aeruginosa* and *S. aureus* was observed in a study of hospitalized CF patients with a small decrease in bacterial density between admission and day 7 of treatment for both the treatment and control groups [39]. A long term study of normal saline vs hypertonic saline similarly showed no difference in *Ps. aeruginosa* density between baseline and either week 24 or 48 values [41].

One study compared topical nebulized tobramycin to placebo in patients with CRS. The study enrolled 21 patients who were refractory to medical and surgical treatment [37]. Quinine at a concentration of 1 mg/ml was added to saline for the placebo group and the tobramycin (active drug product) was also diluted in saline. Both treatments were well-tolerated. Quality of life (QOL) measurement demonstrated a slower decline in the tobramycin group, with a difference that was statistically higher at baseline, week 2, and week 4, but not at the end of the observation period. The higher QOL score at weeks 2 and 4 for the tobramycin group was not qualitatively different from the baseline difference with the placebo, leading one to question whether tobramycin was more effective at any time period. Symptomatic scores for mucosal edema, post-nasal drip, and congestion were lower for the placebo saline/quinine group. Additionally, nasal congestion actually increased during tobramycin treatment whereas congestion decreased at all time-points in the placebo saline/quinine group. Thus, saline/quinine may have been superior to tobramycin nebulized topical treatment for refractory CRS.

Studies of quinine use for leg cramps provides the clearest assessment of potential adverse effects. A 2015 Cochran review of 23 studies comprising 1586 participants provides the most comprehensive analysis [45]. Of note, 5 studies comprising 58% of participants were unpublished reports of drug studies filed with the FDA. Except for the unpublished reports, study quality was generally poor with randomization and blinding methods unclear. Dosing was either 200 or 300 mg/day with treatment lengths ranging between 5 and 28 days, though most gave 14 days of treatment. Quinine-induced adverse effects were grouped into hypersensitivity events and dose-related events [45]. Hypersensitivity events are idiosyncratic and include thrombocytopenia, angioedema, disseminated intravascular coagulation, pancytopenia, and hemolytic uremic syndrome. Dose dependent events and toxicities, such as cardiac abnormalities, gastrointestinal complaints, abdominal pain, tinnitus, vertigo, quinine-induced hypoglycemia, and renal insufficiency, typically did not occur until plasma concentrations of 10 mg/mL or more were achieved. Chronic use of higher doses of quinine can result in cinchonism: a syndrome comprised of tinnitus, dizziness, nausea, and headache. Frequencies of adverse reactions in the Cochrane review are shown in the table below. Minor adverse events were reported in 16 studies and major adverse events were reported as part of 18 studies (Table 1.1.2-2). Withdrawals attributed to transient study drug-associated events were reported for 12 quinine recipients versus 11 placebo recipients. Only one person developed a severe adverse event (SAE) leukopenia, thrombocytopenia, rash, myalgia, and nausea that resolved with stopping of quinine [45].

In summary, quinine administered at doses of 200-300 mg for leg cramps was generally well tolerated. One SAE for hematologic abnormalities was reported out of approximately 806 quinine recipients. Similar findings were reported for an earlier meta-analysis by Man-Son-Hing et al. of a subset of 659 subjects from studies included in the Cochrane Review [46].

Table 1.1.2-2 Adverse events of quinine versus placebo for leg cramps (Cochrane analysis*)

Adverse event	Quinine	Placebo	Relative risk (95% CI)
Minor adverse events			
No. of individuals (16 studies)	725	722	
Any minor event	93 (12.8%)	68 (9.4%)	3% (0-6%)
Gastrointestinal symptoms	39 (5.4%)	16 (2.2%)	3% (1-5%)
Headache	36 (5.0%)	33 (4.6%)	NS
Tinnitus	10 (1.4%)	1 (0.1%)	NS
Pruritus, scaly rash	9 (1.2%)	3 (0.4%)	NS
Dizziness, drowsiness	8 (1.1%)	8 (1.1%)	NS
Myalgia, paresthesia	7 (1.0%)	10 (1.4%)	NS
Visual disturbance	4 (0.6%)	2 (0.3%)	NS
Fever	3 (0.4%)	1 (0.1%)	NS
Major adverse events			
No. of individuals (18 studies)	806	807	
Major event causing study stoppage	12 (1.5%)	11 (1.4%)	NS
Gastrointestinal symptoms	7 (0.9%)	1 (0.1%)	NS
Headache	2 (0.2%)	2 (0.2%)	NS
Tinnitus	1 (0.1%)	0 (0%)	NS
Pruritus, scaly rash	2 (0.2%)	0 (0%)	NS
Dizziness, drowsiness	3 (0.4%)	2 (0.2%)	NS
Myalgia, paresthesia	1 (0.1%)	0 (0%)	NS
Visual disturbance	0 (0%)	1 (0.2%)	NS
Fever	1 (0.1%)	0 (0%)	NS

* Adapted from El-Tawil et al. [45]; NS – not significant.

This study will assess the safety of topical nasal quinine sulfate, dihydrate (6 mg daily) delivered via nasal atomizer and its ability to decrease the incident rate of confirmed SARS-CoV-2 infection. Sterile 0.9% saline will be provided as the placebo control.

1.2 Investigational Agent

GLS-1200 is used as the therapeutic agent in this study. GLS-1200 is formulated as a solution of quinine sulfate, dihydrate (Figure 1.2-1) USP dissolved into sterile normal saline (0.9% sodium chloride) at a concentration of 1 mg/ml and then filter sterilized. Quinine sulfate, dihydrate has a molecular weight of 782.94 g/mol.

Sterile normal saline (0.9% sodium chloride) will be used as the placebo solution in this study.

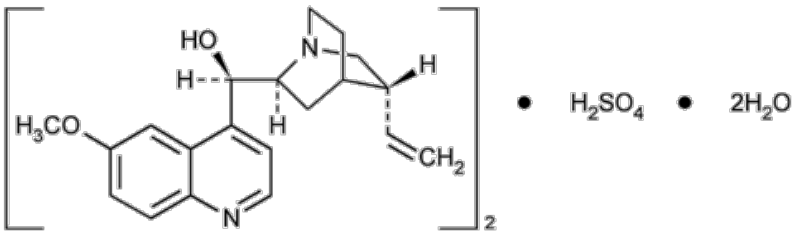

Figure 1.2-1: Structure of Quinine sulfate, dihydrate

1.3 Dose and Regimen Rationale

The dose of quinine sulfate, dihydrate used in this protocol (1 mg/ml) given three times per day via nasal atomizer is similar to that used by Desrosiers et al. [37] (Table 1.1.2-1). Subjects will continue three times daily quinine sulfate, dihydrate usage for 4 weeks. This length of time for quinine exposure is the same as that used by Desrosier et al. (Table 1.1.2-1). The quinine sulfate, dihydrate treatment regime in this protocol is similar to that used in another protocol (IND BB128711) that was reviewed and approved by the University of Pennsylvania IRB (Protocol # 821731).

1.4 Risk/Benefit Assessment

In accordance with the International Conference on Harmonization (ICH), this study has been designed to minimize the risk to study participants. Quinine treatment in this study does not replace or change everyday precautions taken by the study participants in preventing SARS-CoV-2 infection.

Quinine sulfate, dihydrate exposure in this study is 6 mg/day (1 ml of a 1 mg/ml solution used to irrigate each nostril, for total exposure of 2 mg per application, three times daily) and is similar to that used by Desrosiers et al. to study tobramycin vs saline placebo (where the placebo contained 1 mg/ml of quinine to mask taste) [37]. Doses ranging from 2.5 to 90 mg/day have been used as part of various studies for CF (Table 1.1.2-1). As reviewed above, the amount of quinine in an 8 oz. glass of tonic water is greater than 25 mg, while typical doses of quinine prescribed for leg cramps is 200-300 mg/day and for malaria is 1800 mg/day (600 mg three times daily).

The adverse effects of topical quinine are unknown. The adverse effects of orally prescribed quinine include hematologic changes (thrombocytopenia as most common and less commonly anemia) and electrocardiographic effects (particularly prolongation of the QTc). As reviewed, prior clinical studies of nasal or aerosol administered quinine in approximately 750 persons (Table 1.1.2-1) showed no quinine-associated adverse events.

The atomizer provided as part of this study is designed to provide a fine spray into the nose. There is the possibility that the atomizer will not function properly and will cause discomfort when used. Should this occur, study participants are asked to notify the study staff before their next dose. The study staff will discuss continued usage of the atomizer with the participant.

If the GLS-1200 or saline are accidentally sprayed into the eyes, ears or mouth, irritation may occur that could require evaluation. If the syringe and atomizer are not fully connected, the study participant may only receive a partial amount of study drug. If the atomizer or syringe packaging

is found to be open prior to use, it is possible that either component could be contaminated and thus there is a risk for infection. Devices with damaged packaging should not be used.

2. HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

GLS-1200 topical nasal spray administered Day 0 through Week 4 will be safe, well tolerated and reduce the incidence of confirmed SARS-CoV-2 infection.

2.2 Primary Objectives and Outcome Variables

- Evaluate the safety and tolerability of GLS-1200 topical nasal spray
- Incidence of SARS-CoV-2 infection, confirmed by PCR relative to treatment group

2.3 Secondary Objectives and Outcome Variables

- Symptom score of documented SARS-CoV-2 infection relative to treatment group

2.4 Exploratory Objectives

- Incidence of SARS-CoV-2 seroconversion relative to treatment group
- Assess the relationship of taste receptor genetics to incidence of SARS-CoV-2 infection and relative to treatment group

3. STUDY DESIGN

This is a Phase II, placebo-controlled, double-blind study of GLS-1200 topical nasal spray to assess the safety, tolerability, and ability to reduce the incidence of confirmed SARS-CoV-2 infection. Following recruitment and informed consent, those meeting enrollment criteria will be randomized 2:1 (GLS-1200:placebo). Participants will initiate topical nasal spray applications immediately after randomization and will continue for 4 weeks. Participants will self-administer drug three times daily. The primary outcome measurements are safety, tolerability, and reduction in the diagnosis of PCR-confirmed SARS-CoV-2 infection. Follow-up will continue through 6 weeks since some cases of SARS-CoV-2 infection may not be apparent until after the primary treatment period has concluded. Secondary measures will assess the incidence of symptoms between each visit, by treatment group. In addition the average number of days subjects experience each symptom will be summarized by treatment group. Exploratory measures will assess the incidence of seroconversion in serum and the relationship of taste receptor genetics to incidence of SARS-CoV-2 infection both relative to treatment group.

3.1 Safety Monitoring

Subjects will be randomized in a blinded fashion to one of two study treatments (quinine or placebo) at fixed doses. Clinical adverse events (AEs) will be reviewed at each visit up to end of the study. Subjects will be requested to maintain a daily symptom diary to monitor for viral related symptoms and to assess any other potential adverse effects through 2 weeks of follow-up. Safety monitoring will also include laboratory assessment of hematology, chemistry and ECG performed at baseline (pre-treatment) and at Week 4 (end of treatment).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Recruitment of Participants

Adult volunteers will be recruited for the current study.

4.2 Inclusion Criteria

1. Age 18 years or older
2. Able to provide informed consent
3. Able and willing to comply with study procedures
4. Able and willing to utilize an approved form of pregnancy prevention for women of child-bearing potential through to the end of treatment

4.3 Exclusion Criteria

1. Known allergy to quinine, quinidine or mefloquine
2. Confirmed prior positive test for SARS-CoV-2
3. Treatment within the past 2 weeks with chloroquine, hydroxychloroquine, or remdesivir
4. Pregnancy or documentation of pregnancy by pre-treatment urine pregnancy test or breast feeding or plans to become pregnant during the course of the study

4.4 Discontinuation/Withdrawal of Study Participants

Participants will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits. If a participant discontinues the study at any time after enrollment, but prior to the final scheduled study visit, the investigator will make every effort to have the participant complete all assessments. At a minimum, study participants will be encouraged to complete all procedures included in the final study visit should they elect to terminate early. All data collected up to the time of early termination will be used for final analyses except as noted below. Categories of early termination are defined below:

- Voluntary withdrawal from the study: the participant verbalizes or states in writing their desire to withdraw from the study. Data already collected remains as part of the study.
- Lost to follow-up: the participant terminates, does/will not return to complete study visits and cannot be located, or does not respond to written or telephonic contact.
- Withdrawal of consent: the participant provides verbal or written request to withdraw from the study *and* also withdraws consent for use of study data. The investigator is encouraged to discuss withdrawal of consent to ensure that data collected up to the time of study withdrawal can be used for analysis.
- Protocol violation: the participant failed to adhere to protocol requirements. Such events will be discussed between the Medical Monitor and the site PI to determine whether these events constitute a deviation that requires removal of the participant from the study and/or non-use of study data.
- Adverse event (Adverse Reaction): clinical or laboratory events that in the medical judgement of the investigator are grounds for discontinuation for the best interest of the participant. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death: the participant died.

5. STUDY PRODUCT

5.1 Investigational Product

GLS-1200, containing quinine sulfate, dihydrate, USP, the investigational product used in this study, is a small molecule with a chemical structure as shown in Figure 1.2-1. Quinine sulfate, dihydrate, USP will be formulated in 0.9% sterile saline at 1 mg/ml, filter sterilized and provided

to participants in vials with 7.0 ml recoverable volume for daily use. Quinine has been shown to be stable in neutral, weak and strong acid solutions, and weak base solutions, without light exposure for up to 285 days [47]. In contrast, when ultraviolet exposure occurs, the solution's pH influences the rate of decrease in the concentration of quinine: rapid loss in 0.0005N NaOH; much slower decreases in water or strong acids; and the slowest loss in weak solutions of 0.03N HCl [47]. The quinine solution is approximately pH 6 for this study.

Sterile, 0.9% sodium chloride (normal saline), will be used as the placebo solution. Sterile saline will be provided in vials with 7.0 ml recoverable volume for daily use.

5.2 Packaging and Labeling

Study product will be supplied in kits labeled only with a randomly generated Treatment Kit #. Each kit will contain 28 vials of study drug (sufficient for 28 days of treatment) with each vial containing 7 mL of study drug. Study product will be stored at the University of Pennsylvania Investigational Drug Service. Vials of drug will be provided packaged in a cardboard box and inside amber plastic bags to reduce UV exposure.

Drug product labels are shown below in Table 5.2-1. Labels are generated in tandem as shown: one side to be affixed to each Drug Product kit and the second side as detachable for pharmacy logs. As participants present for randomization, treatment assignments will follow the randomization schema in successive order. The study pharmacist will write the Subject ID# and dispensing date on the two labels at the time of study drug dispensation. The side that had been affixed to the Drug Product Kit will remain, while the other half is detached and affixed into the Pharmacy Log form. As noted, the detachable side for Pharmacy is designated as to whether the vials in the kit contain active drug (GLS-1200) or placebo (0.9% saline).

The randomized Treatment Kit # and the designation as Active or Placebo serve as independent confirmatory checks on treatment assignment.

Table 5.2-1 Study drug kit labels

Affixed to Drug Product Kit	**For Pharmacy Log**
Subject ID# _____ Date _____ T2R-002 Study TREATMENT KIT#: **XXXX** GLS-1200 / Placebo 7 ml (#28 vials) Site #101 Uinversity of Pennsylvania Pablo Tebas, MD Store between 2-25ºC (Refrigerated or Room Temp) Expiration Date: MM YYYY Packaged at the University of Pennsylvania, Philadelphia, PA For Investigational Use Only	Subject ID# _____ Date _____ T2R-002 Study TREATMENT KIT#: **XXXX** GLS-1200 / Placebo 7 ml (#28 vials) Site #101 Uinversity of Pennsylvania Pablo Tebas, MD Store between 2-25ºC (Refrigerated or Room Temp) Exipration Date: MM YYYY Packaged at the University of Pennsylvania, Philadelphia, PA For Investigational Use Only **ACTIVE / PLACEBO**

5.3 Handling of Study Drug

Study drug will be stored between 2°C and 25°C in the University of Pennsylvania Investigational Drug Service. Investigational product must be stored in a secure area according to local regulations.

5.4 Dispensing of Study Drug

It is the responsibility of the Investigators that study drug is dispensed only to study participants. Authorized personnel are the only ones to dispense product according to local regulation.

At enrollment, study participants will be provided one kit containing 28 vials of study drug, 28 nasal atomizers, and 84 syringes. Each vial and atomizer will be used for single-day drug administration and then discarded, while a new syringe will be used at each of the three daily administrations and then discarded.

The study pharmacist or study coordinator will demonstrate to participants how to remove drug from the vial into syringes and to self-administer product. Coordinator will also review proper handling and storage conditions for the materials provided. A link will be provided to an instructional video on study drug handling and administration.

5.5 Precautions with Investigational Medicinal Product

Participants will be instructed to keep all unused study drug either refrigerated or at room temperature. Participants will be instructed to keep in-use vials refrigerated at 2-8°C.

5.6 Preparation of Investigational Product

Study product will be supplied in “ready to use” daily-use vials. Sufficient atomizers, vial adapters and syringes will be provided.

5.7 Record of Investigational Product Disposition at Site

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number or batch number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each participant, including unique participant identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount destroyed, if applicable

5.8 Return and Destruction of Investigational Product

Subjects will discard that day’s study drug vial after the third daily dose.

5.9 Device Accountability

The pharmacy will maintain a log to track the lot numbers and distribution of the atomizer used in the study, LMA® MAD NASAL™ Intranasal Mucosal Atomization Device. Participants can discard syringes after dosing both nostrils at each time point and can discard the atomizer after the third daily dose. Unused devices (if applicable) can be discarded at completion of study treatment period.

6. STUDY PROCEDURES AND TREATMENTS

6.1 Procedures by Visit (also see Table S2)

6.1.1 Day 0: Review Study and Eligibility Criteria; Obtain Informed Consent, Enrollment

Subjects will be recruited and provided the informed consent for review. Study staff will review the protocol with the prospective participant and obtain written informed consent. One copy of the informed consent will be maintained at the site, and the other given to the participant.

Study procedures that will be completed include:

- Review medical history, demographics
- Review concomitant medications
- Perform physical exam, height, weight, vital signs
- Perform study ECG, provide order for baseline safety labs (CBC and Basic Metabolic Profile)
- Perform baseline nasopharyngeal swab for viral PCR
- Collect serum for viral antibodies
- Collect saliva for TAS2R genotyping (collection of saliva for genetic testing is optional)
- Provide instruction on self-administration of study drug and device
- Provide study diary

6.1.2 Week 2: intermediate visit

Two weeks into the study participants will return to the study site to complete the following study procedures:

- Review study drug self-administration
- Review new concomitant medications
- Review adverse effects, any new diagnosis of SARS-CoV-2 infection
- Review study diary
- Perform targeted physical exam
- Perform nasopharyngeal swab for viral PCR
- Collect serum for viral antibodies
- Collect plasma for quinine measurement

6.1.3 Week 4: end of treatment

Study procedures that will be completed include:

- Review new concomitant medications
- Review adverse effects, any new diagnosis of SARS-CoV-2 infection
- Perform targeted Physical exam
- Review study diary
- Perform nasopharyngeal swab for viral PCR
- Perform ECG
- Perform repeat safety labs (CBC and Basic Metabolic Profile)
- Collect serum for viral antibodies

6.1.4 Week 6: follow up visit

Study procedures that will be completed include:

- Review new concomitant medications
- Review adverse effects, any new diagnosis of SARS-CoV-2 infection

- Review and collect study diary
- Perform targeted physical exam
- Perform nasopharyngeal swab for viral PCR
- Collect serum for viral antibodies
- Collect and review diary

6.2 Timing and Evaluations

6.2.1 Informed Consent (Day 0)

Study personnel will meet with prospective study participants, explain the study, and provide them with an informed consent form (ICF) that describes the eligibility criteria for entering the study, study treatments and follow-up procedures. An informed consent must be signed prior to any study related procedures being performed. A copy of the signed and dated consent form will be given to the participant.

6.2.2 Enrollment (Day 0)

Participants who consent to be in the study will be assigned a unique participant identification designation number (PID#). Once assigned, PID numbers cannot be reused for any reason. Information regarding participant's PID# and screen date will also be documented on a screening log. See section 8.7 for allocation schedule and process.

Medical History

Investigators should document all significant illnesses that the participant has experienced as Medical History in the last 6 months. Illnesses' first occurring or detected during the study and/or worsening of an existing illness that occurs after the first administration of study drug are documented as AEs on the electronic case report form (eCRF).

Prior and Concomitant medications

Prior treatments, defined as administered up to 8 weeks prior to the time of informed consent, will be recorded in the eCRF as prior medications. Concomitant treatments, defined as continuing or new treatments taken at or after the signing of the informed consent, will be recorded in the eCRF as concomitant medications.

Review of study drug self-administration

Study staff will review with the participant the procedures for self-administration and provide a link for an instructional video.

Provide study drug and diary

Study staff will provide participants with a kit containing study drug, syringes, and atomizers for 28 days of treatment. A study diary will be provided and instructions on how to complete the diary will be reviewed.

6.2.3 Safety Assessments

6.2.3.1 Adverse effects

Adverse effects will be queried at the Week 2, 4, and 6 visits.

6.2.3.2 Physical Assessments and Targeted Physical Assessment

A physical examination will be performed at study enrollment and a targeted physical examination will be performed at the Week 2, 4 and 6 visits and any unscheduled visit.

6.2.3.3 Vital Signs

Participant vital signs will be performed at all study visits.

6.2.3.4 Weight and Height

Participant height and weight will be assessed and recorded at enrollment.

6.2.3.5 12-lead ECG

A 12-lead ECG will be performed at enrollment and at the Week 4 visit.

6.2.3.6 Safety Laboratory Evaluations

Blood draws for a complete blood count with differential and a basic metabolic panel (consisting of sodium, chloride, potassium, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine, and glucose) will be performed at baseline and at the Week 4 visit.

6.3 Assessment of Laboratory Abnormalities

Serum chemistries (basic metabolic panel) and complete blood count with differential blood count will be graded as noted in Section 7.1.

6.4 Assessment of Clinical Adverse Events

Participants will also be queried regarding the occurrence of any adverse events, concomitant medications and new onset disease during their clinic visits. Participants will be reminded to contact study personnel and immediately report any event that may happen for the duration of the study up to and including the final study visit. Events will be recorded in eCRF.

The Investigator will grade clinical AEs (based on discussions with study participants) using the NCI Common Terminology Criteria for Adverse Events v5.0. Laboratory abnormalities of grade 2 or higher will be captured.

6.5 Nasopharyngeal swab PCR for presence of SARS-CoV-2 virus

Nasopharyngeal swabs will be performed at baseline and Weeks 2, 4 and 6 to perform PCR to document the presence of SARS-CoV-2 virus RNA, which may be done by research use only (RUO) assays.

Results of the Nasopharyngeal Swab

Results of the nasopharyngeal swab may be received as soon as one day after testing.

If the PCR results are positive for SARS-CoV-2 infection at enrollment, the participant will be asked to remain in the study, administer study drug as per protocol, comply with all required testing for safety, and complete the remaining visits. If the participant does not want to administer study drug or complete testing, they will be asked to consent to telephone contact for the remaining visits.

6.6 Serum for SARS-CoV-2 antibodies

Serum will be collected at baseline and Weeks 2, 4 and 6 to measure SARS-CoV-2 antibodies using RUO assays.

6.7 Definition of confirmed SARS-CoV-2 infection and SARS-CoV-2 symptom score

Participants will be queried as to any new diagnosis of SARS-CoV-2 infection, defined as a positive PCR test for SARS-CoV-2. This definition is consistent with the current protocol for viral PCR testing. All deaths will be considered as treatment failures.

Participants will also be instructed to maintain a symptom diary that includes those symptoms considered common for SARS-CoV-2. The diary is inclusive of symptoms identified by the World Health Organization for a diagnosis of SARS-CoV-2 as well as more recently identified symptoms such as conjunctivitis, diarrhea, and loss of taste or smell. Each symptom will score scored as present (score of 1) or absent (score of 0) for each two week interval and the incidence of each symptom will be summarized by treatment group. In addition, the average number of days subjects had each symptom throughout the study period (6 weeks) will be summarized by treatment group.

6.8 Exposures to SARS-CoV-2

Exposure history to patients known to have SARS-CoV-2 will be included as part of the participant diary.

6.9 Saliva for *TAS2R* genotyping

Samples of saliva will be collected for genotype analysis of the bitter taste receptors (T2R) using chip technology that includes known common *TAS2R* single nucleotide polymorphisms (SNPs). Dense genotyping, after purification and quantification of genomic DNA, will interrogate and genotype 96 of the T2R SNPs with high minor allele frequency (mostly missense). The results of genotype analysis of T2Rs that are stimulated by quinine will serve as an exploratory co-variate of treatment outcome and be presented as a descriptive analysis. This data is for study purposes only and will not be entered into the participants' clinical record.

7. EVALUATION OF SAFTY AND MANAGEMENT OF TOXICITY

7.1 Safety Parameters

7.1.1 Adverse Events (AEs)

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical conditions/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment.

An unexpected AE is:

- Not identified in the Investigator's Brochure (IB) or otherwise not expected from the characteristics of the clinical material
- Not listed at the specificity or severity that has been previously observed

Study related AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE
- Complications and termination of pregnancy; see Section 7.1.8 for additional information.
- All AEs that occur after enrollment and throughout the duration of the study will be recorded.

Study related AEs do not include the following:

- Elective medical or surgical procedures
- Non-elective medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before study enrollment that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the first dosing and not related to a protocol associated procedure is not an AE. It is considered to be pre-existing and will be documented on the medical history eCRF
- Any laboratory abnormality that is considered as non-significant or considered as related to another non-study related condition
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

7.1.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., participant was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation. However, hospitalization (including hospitalization for an elective procedure) for continued treatment or assessment of a pre-existing condition that has not worsened, does not constitute an SAE. NOTE: Evaluation in a physician's office, or at a hospital or other urgent care setting in an observational, non-admitted status regardless of the time period of observation, does not constitute an SAE;
- Results in congenital anomaly or birth defect;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself
- The participant may not have been on investigational medicinal product at the occurrence of the event.
- "Life-threatening" means that the participant was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE
- Inpatient hospitalization means that the participant has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. Observation status or evaluation in an emergency department, urgent care setting, or outpatient office does not constitute an SAE.
- The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution. The reporting period for SAEs is described in Section 9.6.2.

7.1.3 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction is a reaction for which the nature or severity is not consistent with the applicable product information (see Investigator's Brochure). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events.

7.1.4 Assessing Severity (Intensity)

The Investigator will grade laboratory AEs and clinical AEs (based on discussions with study participants) using the NCI Common Terminology Criteria for Adverse Events v5.0:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Life-threatening consequences (Grade 4)
- Death related to AE (Grade 5)

Adverse events will be recorded on the eCRF at the severity reported by the investigator.

If an ongoing AE worsens or increases in its severity or its relationship to the study drug changes, a new AE entry for the event should be entered on the eCRF.

The following is a link to the grading scale:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

7.1.5 Causal Relationship of Investigational Product to Adverse Events

A causally related AE is one judged to have a suspected relationship to the administration of the investigational agent. Conversely, an AE may also be assessed as not related to the investigational product. The Investigator is responsible for reporting adverse events and judging

the relationship between the administration of the investigational product and an AE because the investigator is knowledgeable about the participant (e.g., medical history, concomitant medications), administers the investigational product, and monitors the participant's response to the investigational product. The Sponsor will assess the overall safety of the investigational product and determine whether expedited reporting to regulatory agencies is indicated.

Investigators should use their knowledge of the Study Participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug by the following criteria:

- Related – the investigator considers that there is a causal relationship between the event and study drug;
- Probably related – the Investigator considers that there is a probability of a causal relationship of the event to the study drug
- Possibly related – the investigator considers that there is a possible causal relationship of the event to the study drug
- Not related – the investigator considers that the event has no relationship to administration of the study drug

The following guidance should also be taken into consideration:

- Temporal relationship of event to initiation of study drug;
- Course of the event, discontinuation of study drug, or reintroduction of study drug (when applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Participant or use of concomitant medications known to increase the occurrence of the event

7.1.6 Abnormal Laboratory Value

Grade 2 and higher laboratory abnormalities (e.g., serum chemistry, CBC) are to be recorded.

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

7.1.7 Pregnancy During Study

Pregnancy is an exclusion criterion for participation in this study. Women of childbearing potential should either be unable to conceive or use a form of birth control such as a diaphragm, birth control pills, IUD, or regular use of male or female condom. If a participant becomes pregnant during the time of the study, they will be asked to contact study staff after the end of the study to report on the outcome of pregnancy.

7.1.8 Post-study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for participants on study (including any protocol-required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for participants. However, if the Investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the Investigator to be probably or possibly related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.2 Methods and Timing for Collection and Recording of Safety Data

At the time of each study visit, participants will be queried as to adverse events that have occurred in the interim period and the current status of any AE that was reported at a prior visit that has not yet resolved. As delineated above, both solicited and non-solicited events will be sought. Additionally, labs and ECGs will be reviewed for safety.

All AEs, regardless of severity, seriousness, or presumed relationship to study treatment, must be recorded using medical terminology in source documents and on the eCRF. Whenever possible, a diagnosis will be documented, in lieu of symptoms. The source document and the eCRF must contain the Investigator's opinion concerning the relationship of the AE to study treatment.

AEs should be described with the following attributes:

- Duration (start and end dates)
- Seriousness
- Severity
- Causality
- Action(s) taken
- Outcome

7.3 Safety and Toxicity Management

The Medical Monitor will be responsible for the overall safety monitoring of the study. The site Investigator will be responsible locally for safety.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class, preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters

7.3.1 Events Requiring Expedited Reporting

Events requiring expedited reporting (ERER) are defined as any Adverse Events including:

- Grade 3 or greater fever;
- Grade 3 or greater systemic symptoms;
- Grade 3 or greater laboratory abnormalities

The most severe grade for that particular event is to be documented in the eCRFs.

Sites will inform the Sponsor of any ERER within 24 hours to discuss whether dosing to the participant should continue.

7.3.2 Stopping Rules

If any of the following situations occur, then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator and the IRB (if applicable):

- Three (3) or more participants experience an ERER assessed as related to Study Treatment;
- Any participant experiences a potentially life threatening AE, Grade 4 AE or death assessed as related to Study Treatment;
- Five (5) or more participants across both treatment arms experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Any report of anaphylaxis of Grade 3 or greater assessed as related to Study Treatment.

Upon conclusion, the sponsor or designee will notify all investigators and the IRB/REC (if required) regarding the outcome of any investigation.

Any SAE or death assessed as related to Study Treatment will lead to an immediate halt of study enrollment and Study Treatments, until the event has been investigated and Sponsor has consulted with FDA.

Study restart will occur following approval of the IRB/REC and/or FDA as applicable.

Guidelines for assessing relatedness are detailed in Section 7.1.5.

7.3.3 Unblinding

This is a double-blind study.

Emergency unblinding for AEs may be performed. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. Unblinding should only be considered for the safety of the patient. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the patient's treatment allocation after discussion and approval by Sponsor Medical Monitor. The Investigator must note the date, time, and reason for unblinding. The Investigator should inform the Sponsor that the patient was unblinded, however they are not required to reveal to the Sponsor the patient's treatment allocation.

Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Ethics Committees, and/or IRBs.

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

8. STATISTICAL METHODS and CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

8.1 Data Sets to be Analyzed

Any participant who is randomized to a treatment allocation will be considered part of the intention-to-treat (ITT) population. The ITT population will be used for the summary of all demographic and baseline characteristics and for analysis of the primary outcome. Subjects lost to follow-up, requiring rescue therapy, those who discontinue study prior to completion of the primary treatment

end point (Week 4) and those who test positive for SARS-CoV-2 infection at Weeks 2 or 4 will be considered as treatment failures. Separate analysis will examine treatment failures in the period between the cessation of study treatment (Week 4) and the end of study (Week 6). All deaths will be considered as treatment failures. All subjects will be grouped in analyses and summaries based on their randomization allocation. The following analysis populations will be defined from the ITT population:

- The safety analysis set includes all randomized participants and is synonymous with the ITT set except that patients will be grouped based on treatment actually received.
- Per-protocol (PP) analysis set includes all participants who complete the trial and who receive ≥90% Study Treatments through to either diagnosis of SARS-CoV-2 infection (study end point) or to end of study for those without a SARS-CoV-2 diagnosis, based on subject completed accountability logs, and have no significant protocol violations. Participants in this sample will be grouped to treatment arms they actually received. This set will be used as a sensitivity analysis to summarize the primary and secondary efficacy outcomes.

8.2 Demographic and Other Baseline Characteristics

Demographic and baseline data, vital signs, medical history, concomitant illnesses, and current medications/treatments will be summarized by means of descriptive statistics: continuous variables as mean, median, standard deviation, and interquartile ranges and categorical variables as frequencies and percentages, stratified by treatment arm based on the ITT population.

8.3 Safety Analysis

All safety and tolerability summaries will be performed on the safety analysis population.

8.3.1 Adverse events

Treatment emergent AEs will be summarized by frequencies and will be presented by system organ class and preferred term with the number and percentage of participants affected. Frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment.

The proportion of participants experiencing any AEs (Grade 1-4) following treatment with study drug will be presented as part of the safety analysis set. The precision with which this sample result estimates the rate of similar AEs in the population represented by the study sample will be reported in terms of 95% confidence intervals (CI) around the sample proportions. This will provide 95% confidence that the rate of severe adverse effects is not greater than the upper limit of the CI around the proportion of participants with grade 3+ events in the study sample.

8.3.2 Laboratory Data

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values. Categorical response variables will be summarized per time point with percentages.

8.4 Efficacy Analysis

The primary efficacy analysis is the difference between groups of confirmed SARS-CoV-2 infection as based on the ITT analysis population.

8.5 Secondary Analysis

Secondary outcomes will be summarized as to the incidence of each symptom by treatment group and the average number of days each symptom was present over the course of the study (6 weeks). Summaries will be presented, noncumulatively by visit and well as cumulatively over 4 weeks of treatment.

8.6 Interim Analysis

No interim analysis is planned.

8.7 Sample Size and Randomization

The sample size for this study is based on an infection rate in the placebo group of 10%. A 2:1 randomization of 225 subjects would have a power of 80.8% to detect a difference of 9% between groups at alpha = 0.05 assuming 1% of individuals in the treatment group was confirmed to be infected with SARS-CoV-2. Table 8.7-1 below provides a range of treatment rates that could be detected with at least 80% power using this sample size.

Table 8.7-1 Range of treatment rates detectable with at least 80% power

Treated Infection Rate (N=150)	Placebo Infection Rate (N= 75)	Difference Treated - Placebo	Actual Power
0	7.3%	-7.3%	80.3%
1%	10%	-9%	80.8%
2.5%	13.5%	-11%	80.3%
5%	18.1%	-13.1%	80.4%
7.5%	22.1%	-14.6%	80.3%
10%	25.7%	-15.7%	80.0%

8.8 Missing Values

If a subject is lost to follow-up, or for some reason fails to provide an assessment of the primary endpoint, the subject will be considered a treatment failure per the ITT population.

9. DATA COLLECTION, MONITORING, AND AE REPORTING

9.1 Confidentiality

Information about study participants will be kept confidential to the best of the study site's ability.

In the event that a participant revokes authorization to collect or use personal health information (PHI), the sponsor retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include (as applicable): hospital records, clinical and office charts, laboratory notes, memoranda,

participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, pharmacy records, laboratory records, medical records (including electronic records) relative to the clinical trial.

9.3 Data Collection

Data will be collected using Electronic Data Capture (EDC). Participants will be identified by PID#. Initial data collection may utilize a paper form of the EDC. Any such records will be maintained as source data.

9.4 Record Retention

It is the Investigator's responsibility to retain study essential documents as per country regulations: in the US for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.5 Safety and Quality Monitoring and Record Availability

Monitoring

Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor as outlined in the Monitoring Plan.

Record availability and auditing

The investigator will make study documents (e.g., ICFs, drug accountability forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, regulatory agencies, GeneOne Life Science, Inc. or its designee for confirmation of the study data.

Participation as an investigator in this study implies acceptance of potential inspection by regulatory authorities and applicable compliance and quality assurance offices.

9.6 Adverse event (AE) Reporting

To assure the safety of the participants, information about all AEs, whether volunteered by the participant, discovered by investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the participant's source documents and followed as appropriate.

A summary of the study's overall progress will be forwarded to regulatory agencies according to the local requirements.

9.6.1 Study Reporting Period of Adverse Events

Solicited and unsolicited AEs will be collected throughout the study and recorded.

9.6.2 Study Reporting Period for Serious Adverse Events

SAEs occurring from the time of consent through to the end of the study are to be reported without regard to causality. SAE's should be reported to GeneOne Life Science within 24 hours of discovery. Investigators should also report SAEs to their local IRB/REC as required.

Expedited reporting of SAEs will be determined by GeneOne Life Science using reference safety information specified in the Investigator's Brochure. An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.4 (Suspected Unexpected Serious Adverse Reaction, SUSAR) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the Ethics Committee as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

At any time after completion of the SAE reporting period, if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor or its designee.

If the Investigator becomes aware of an SAE after the last scheduled follow-up contact, and considers the event related to prior Study Treatment, the Investigator will report it to GeneOne Life Science.

SAE TELEPHONE AND CONTACT INFORMATION:

MEDICAL MONITOR:	Joel Maslow, MD PhD MBA
PHONE:	(484) 965-9147p; (610) 331-7844 c
MEDICAL LIAISON:	Celine Remigio, RN DPT
CELL:	(914) 606-1199
EMAIL:	cremigio@geneonels-us.com
24 hr Answering Service	(215) 703-5843
GeneOne FACSIMILE:	(484) 965-9146
GeneOne Safety Email	GeneOneSafety@geneonels-us.com

MAILING ADDRESS:
GeneOne Life Science, Inc.
1040 DeKalb Pike
Suite 200
Blue Bell, PA 19422

The report should contain as much clinical safety information as possible, but at minimum, the initial report must include the following information:

- Participant number and Study name
- Date of Onset and Date of Resolution (if applicable)
- Detailed description of event
- Investigational product (if known)
- Causal relationship of event to investigational product
- Reporter name and contact information

Follow-up reports will be sent as soon as more information becomes available. Events for which the study participant seeks medical care, the study site will attempt to obtain relevant medical records to include as source documents. These include but are not limited to discharge summary, results of relevant laboratory tests, and reports of relevant radiographic studies. In the case of death, the investigator will attempt to procure relevant reports (such as autopsy reports, medical examiner report, discharge summary).

Each SAE must be followed by the investigator until resolution, stabilization, or return to baseline, even if this extends beyond the end of the study, with follow-up report filed to provide a summary of the event through resolution.

The original SAE form must be kept at the study site. Copies (or electronic copy) will be provided to GeneOne Life Science or its representative, who will be responsible for reporting to regulatory authorities as indicated, and copy will be forwarded to the study sites IRB/REC.

9.6.3 Notification of Serious Adverse Events

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected (e.g., FDA Form 3500A in the US). Reports of SAEs shall be made as soon as possible and in no event later than 15 calendar days after the Sponsor's initial receipt of the information. Written notification may be submitted on the form described above or equivalent or in a narrative format and shall bear prominent identification of its contents. Each written notification to regulatory agencies shall be transmitted to the division that has responsibility for review. In each written safety report, the Sponsor shall identify all safety reports previously filed concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports. The Sponsor shall also notify the relevant regulatory authorities by telephone, facsimile, or email transmission of all deaths and any unexpected fatal or life-threatening experience, regardless of causality, as soon as possible but in no event later than 7 calendar days after the Sponsor's initial receipt of the information. Each telephone call or facsimile transmission to regulatory agencies shall be transmitted to the division that has responsibility for review.

Follow up information to a safety report shall be submitted as soon as the relevant information is available. If the results of a Sponsor's event investigation show that an adverse drug experience not initially determined to be reportable is, in fact, reportable, the Sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of investigations of other safety information shall be submitted, as appropriate, in an information amendment or annual report. In the event of death, if an autopsy is performed, a copy of the report, redacted for PHI but labeled with the PID#, should be sent to GeneOne Life Science, Inc.

9.7 Study Discontinuation

GeneOne Life Science reserves the right to discontinue the study for safety or administrative reasons, including lack of enrollment, at any time. Investigational product must be returned to GeneOne, unless instructed otherwise. Document retention will follow local regulation.

10. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be allowed. Any proposed presentation, abstract and/or manuscript must be made available to GeneOne at least 60 days prior to submission. GeneOne shall have fifteen (15) days for review. If GeneOne considers that material would reveal protectable intellectual property, GeneOne may request a delay in submission for a maximum of three (3) months from the date of receipt in order for patent application(s) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

11. LIST OF ABBREVIATIONS

AE Adverse event

ALI Air-liquid-interface

AVI	Alanine-valine-isoleucine, non-functional TAAS2R38 allele
BUN	Blood urea nitrogen
CBC	Complete blood count
CBF	Ciliary beat frequency
CF	Cystic fibrosis
CI	Confidence interval
CRS	Chronic rhinosinusitis
DAF-FM	4-amino-5-methylamino-2',7'-difluorescein
eCRF	Electronic case report form
EDC	Electronic data capture
ERER	Event requiring expedited reporting
IB	Investigator's brochure
ICF	Informed consent form
IRB	Investigation review board
ITT	Intention-to-treat
L-NAME	L-N^G-nitroarginine methyl ester
MOI	Multiplicity of infection
NO	Nitric oxide
NS	Not stated
PAV	Proline-alanine-valine, functional TAS2R38 allele
PHI	Personal health information
PID#	Participant identification designation number
PP	Per-protocol
PTC	Phenylthiocarbamide
QOL	Quality of Life
RUO	Research Use Only laboratory assay
SAE	Serious adverse event
SAP	Statistical analysis plan
SCC	Solitary chemosensory cells
SNP	Single nucleotide polymorphism
SUSAR	Suspected unexpected serious adverse reaction
TAS2R	Type 2 taste receptor, bitter taste receptor
TID	Thrice daily
USP	United States pharmacopeia

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