Phase 1 Clinical Trial of a Q GRFT Nasal Spray

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LIST OF ABBREVIATIONS AND ACRONYMS

ADA	Anti-drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
API	Active Pharmaceutical Ingredient
BID	Twice daily
BSIT	Brief Smell Identification Test
FIH	First in Human
GRFT	Griffithsin
IV	Intravenous
IRB	Institutional Review Board
MERS	Middle Eastern Respiratory Syndrome
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
PBS	Phosphate-buffered Saline
PCR	Polymerase chain reaction
SARS	Severe Acute Respiratory Syndrome
SID	Once daily
SOP	Standard operating procedure(s)

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Phase 1 Clinical Trial of a Q GRFT Nasal Spray
PREVENT COVID 101

PROTOCOL SUMMARY

Short Title: PREVENT COVID 101

Protocol Chair: Katherine Bunge, MD

Sample Size: 45 evaluable participants.

Study Population: SARS CoV-2 vaccinated, healthy, 18 – 55 years old

Study Sites: UPMC Magee-Womens Hospital, Pittsburgh, PA

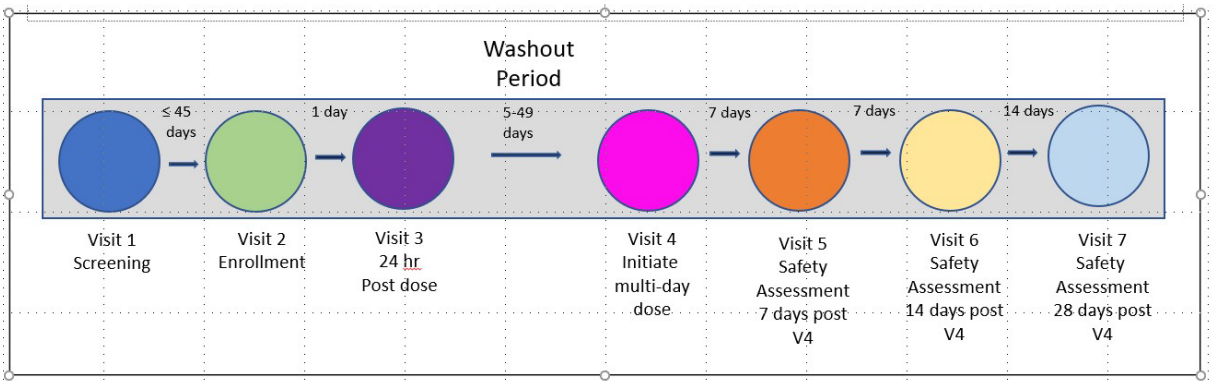
Study Design: A phase I randomized, placebo-controlled, single site safety study

Study Duration: Accrual of approximately 45 evaluable participants is expected to take 6 months. The expected duration of study participation for each participant will be approximately 6-8 weeks. This includes the screening period.

Study Products: Q-GRFT Nasal Spray (7.5mg/mL) and Placebo Nasal Spray. 2 sprays of 100µL each nostril, total of 3mg Q-GRFT per administration

Study Regimen: All participants will apply two metered doses of Q-GRFT in each nostril (400µl total). The spray will be administered by a clinician on the day of enrollment. Participants will be monitored in the clinic for 1 hour after administration and return for a 24-hour post dose visit. If safe and acceptable, a second period of daily administration for 13 days will commence. Safety assessments will be performed at day 7, day 14, and day 28 visits after the initiation of the second period. Additional safety assessments will be done by contacting participants between visit 4 – 5 and visit 5 –6.

Study Schema:



Note: the window between V1 and V2 has been increased to 60 days

Primary Objectives:

- To assess the local and systemic safety of intranasal Q-GRFT after 14 doses

Endpoints:

- The proportion of participants who experience a related Grade 2 or higher adverse event

Secondary Objectives:

- Persistence: To determine the persistence of Q-GRFT in the respiratory tract after a single dose and after 13 days of daily use as assessed by nasopharyngeal swab
- Pharmacokinetics: To determine the systemic absorption of Q-GRFT after administration of a single dose and after 13 days of daily use
- Acceptability: To assess the acceptability of a Q-GRFT nasal spray

Secondary Endpoint:

- Persistence: Q-GRFT concentrations from nasopharyngeal swabs collected 24 hours after a single dose and 24 hours after 13 consecutive daily doses
- Pharmacokinetics: Q-GRFT concentrations in plasma 24 hours after the first dose and 24 hours after the 13th consecutive daily dose
- Acceptability: Self-reported assessment of qualities of the experience with the nasal spray through a Likert scoring of acceptability questions

Exploratory Objective:

- To assess the impact of Q-GRFT nasal spray on smell
- Persistence: Q-GRFT concentrations from oropharyngeal and nares swabs collected 24 hours after a single dose and 24 hours after 13 consecutive daily doses
- Presence of Q-GRFT in the gastrointestinal tract after 13 days of consecutive use
- To determine the potential of the Q-GRFT study drug product to induce an immune response by measuring the generation of anti-drug antibodies (ADAs) in plasma/blood samples after multiple Q-GRFT intranasal spray treatments

Exploratory Endpoint:

- Change in Brief Smell Identification Test (BSIT) score after 13 days of consecutive daily doses compared to baseline
- Persistence: Q-GRFT concentrations from oropharyngeal and nares swabs collected 24 hours after first dose and 24 hours after the 13th consecutive daily dose
- Presence: Q-GRFT concentrations from rectal swab collected 24 hours after the 13^{th} consecutive daily dose
- Immunogenicity of Q-GRFT study product delivered by an intranasal spray system
- Humoral antibody responses to Q-GRFT in plasma/blood by ELISA

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase 1 Clinical Trial of a Q-GRFT Nasal Spray

Short Title: PREVENT COVID 101

1.2 Funding

Funding Agency: National Cancer Institute
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2 INTRODUCTION

2.1 COVID-19

The pandemic due to Coronavirus disease-19 (COVID-19) caused by SARS-CoV-2 has led to more than 4.7 million deaths globally and 688,000 deaths in the US as of September 27, 2021[1]. SARS-CoV-2 transmission occurs predominantly through oral and nasal routes leading to high viral replication in the oropharynx and nasopharynx.

2.2 Q-GRFT

Q-GRFT is derived from Griffithsin (GRFT) which is a non-glycosylated protein consisting of 121 amino acids. Q-GRFT contains a single amino acid substitution, M78Q variant, resistant to oxidation yet maintains the parent molecule's pharmacological profile.

Q-GRFT is obtained from Nicotiana benthamiana plants. It targets mannose residues on the surface of viral glycoproteins with nanomolar affinity and neutralizes a broad spectrum of coronaviruses. Studies in human bronchial airway epithelium cultures (EpiAirwayTM – AIR-100) confirm that Q-GRFT inhibits SARS-CoV-2 infection. Intranasal and inhalation griffithsin (GRFT) has shown protection against SARS and MERS respectively in animal models. Over the past 17 years, three coronaviruses of the Betacoronavirus genus have emerged as serious human pathogens. Coronavirus envelope Spike proteins (S) are very heavily glycosylated, with each spike trimer displaying 66 N-linked glycans in SARS-CoV-2, 69 in SARS-CoV and 75 in MERS-CoV. GRFT and Q-GRFT inhibits viral entry of all coronaviruses tested, including SARS-CoV, MERS CoV and SARS-CoV-2. Moreover, delivery of GRFT to the upper respiratory tract provides significant protection from SARS-CoV, MERS-CoV and paramyxovirus Nipah virus in animal models. Q-GRFT is being investigated for prevention of SARS-CoV-2 infection and is administered intranasally for this indication.

2.3 Rationale

This is a phase I randomized, placebo-controlled, single site safety study. This is a first in human multi-day dose clinical trial of the intranasal formulation. The intranasal formulation of this compound could provide an effective prophylactic for SARS-CoV-2 infection. Furthermore, this product addresses a much larger need of ensuring that the community is equipped with broadly effective antiviral products in the event of the emergence of new coronaviruses. The broad-spectrum activity of Q- GRFT could provide protection not only against SARS-CoV-2, but also any future threats from similar viral pathogens. This product is highly applicable to frontline healthcare workers and at- risk populations, including those that are not responsive to vaccines, such as immunocompromised people. We hypothesize that prophylactic use of Q-GRFT against SARS-CoV-2 via a nasal spray can lead to virus inactivation at the sites of viral entry and replication.

2.4 Safety Data: Q-GRFT

Pre-Clinical Safety

The safety profile of GRFT and Q-GRFT lectins in PBS, saline enema solution and rectal gel formulations was found to be excellent. Various published studies had shown absence of immunotoxicity in vitro and in murine models[2-4]. GRFT and Q-GRFT are not mitogenic, do not activate T-cells, and induce very little alteration in secretion of inflammatory cytokines in treated PBMC from 11 different human donors[2,4] (IND 130697 Module 4 Study Report UL-20180925). These studies also showed no production of inflammatory cytokines in mucosal secretions of rabbits treated with free API and mice treated with GRFT gel formulations.

Upon repeated administration GRFT and Q-GRFT induce antibody responses at low titers. However, GRFT polyclonal antibodies raised in rabbits do not neutralize GRFT's antiviral activity (D. Montefiori and K.E. Palmer, unpublished). More importantly, Q-GRFT was found to elicit a

systemic antibody response only in the rabbit model and not in rat after 21 consecutive days of once-daily intrarectal administration of Q-GRFT gels (IND 130697 Module 4 Study Reports UL-20180126 and UL-20180416). However, there was no localized or systemic toxicity observed at any dose of drug administered. Hence, Q-GRFT is immunogenic but is not immunotoxic (IND 130697 Module 4 Study Report M334-17). Moreover, studies described in IND 130697 Module 2 Sections 2.6.2 and 2.6.4, show that despite these developments, effective antiviral concentrations of drug remain in situ after intrarectal application of Q-GRFT (gel or saline enema formulations). Intranasal Q-GRFT delivery to rabbits showed ADA in few animals (M495-21), but none in the rat model (Study 1901-005). These results further suggest the species difference and the observed immunogenicity is likely due to the sensitivity of rabbit model.

The toxicology program for Q-GRFT for IND 130697 assessed gels at 0.3%, 1.0% and 3.0% drug concentrations in multi-species studies. No toxicity was observed in any model at any dose of drug evaluated. Extrapolating to humans, the 1.0% concentration in a gel (10 mg/mL drug) delivered at 4 mL application volume, equates to a 40 mg Q-GRFT dose. This level of drug was selected as the clinical dose as it was flanked by lower and higher concentrations in nonclinical safety studies, none of which showed toxicity. The drug formulation for clinical administration was changed during development from a gel to a saline enema due to gel compatibility issues with condoms. Hence, the saline enema solution was administered in a Phase 1 clinical study: PREVENT HIV consists of 40 mg Q-GRFT in 125 mL final volume.

Intranasal administration of Q-GRFT nasal spray has been tested in rats and rabbits in Good Laboratory Practice (GLP)-compliant toxicity studies. Additionally, genotoxicity was assessed in a mouse micronucleus assay and ocular irritation was assessed in NZW rabbits.

Study 1901-005 was a 30-day repeat dose study in CD® rats with a 14-day recovery period. Q-GRFT (7.5 mg/mL) was administered by intranasal instillation once daily (SID) or twice daily (BID). Control groups included SID and BID vehicle control (formulation without Q GRFT) and negative control groups (phosphate-buffered saline only). The dose was 0.3375 mg Q-GRFT per administration (0.3375 mg/day for the SID group; 0.675 mg/day for the BID group), corresponding to approximately 1X and 2X the planned human dose on an API (mg Q GRFT) per nasal surface area basis. The second dose for the BID groups was administered 12 hours after the first dose. Evaluations included mortality, clinical signs, body weight, food consumption, ophthalmology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), toxicokinetic parameters, anti-drug antibody parameters, organ weights, and macroscopic and microscopic examinations. Results show no Q GRFT related effects on any parameter examined.

Once or twice daily intranasal administration of Q-GRFT for 30 days at dose levels of 0 (placebo) and 0.3375 mg/dose (0, 0.3375, and 0.675 mg/day) to Sprague-Dawley rats resulted in no test article-related findings for evaluated parameters (mortality, clinical signs, or effects on body weight or macroscopic findings); as well as a lack of immunogenic response. The No-Observed-Adverse-Effect-Level (NOAEL) was considered to be 0.675 mg/day (0.3375 mg/dose BID). On Day 30, the mean Cmax values at the NOAEL were BLQ and 4.20 ng/mL, for males and females respectively.

Study M495-21 is a fifteen-day repeat-dose intranasal and intravenous toxicity study of Q-GRFT in New Zealand White Rabbits with a two-week recovery period. Immunogenicity and toxicokinetics assessment was conducted to determine potential toxic effects, identify target organ of toxicity, and estimate the maximum tolerated dose (MTD) and the NOAEL of test article following a single-day (Interim Arm, Phase A) or once daily intranasal or intravenous (IV) dose administration to New Zealand White rabbits for 15 days followed by a two-week recovery period (Main and Recovery Arms, Phase B).

The IV route of administration was proposed to determine the potential systemic toxicity of the test article and allow the highest dose of the test article to be administered. The test articles for IV

administration was Q-GRFT in Phosphate-buffered Saline (PBS) and corresponding vehicle. IV arms included vehicle control Group 2 (IV vehicle, 0 mg API) and Q-GRFT IV treatment Group 5 (IV, 1.29 mg API, corresponding to approximately 10X the proposed human intranasal dose on a weight basis).

The intranasal route is the proposed route for prevention of SARS-CoV-2 in humans. The test articles used for intranasal administration in this study matches the clinical drug product formulation and corresponding vehicle control. Intranasal dose treatment of vehicle control was administered on Day 1 to animals in Group 1 (intranasal vehicle, 0 mg API), and test article Q-GRFT was administered to Group 3 (intranasal, 1.5 mg API; approximately 1.5X the human intranasal dose on a mg/surface area basis) and Group 4 (intranasal, 3 mg API; 3X the human intranasal dose on a mg/surface area basis). Each intranasal -dose volume was administered in 0.05 ml treatment increments alternating briefly, pausing between nares to deliver the entire volume. Each treatment group consisted of a single dose arm (Phase A) and a 15-day multidose arm (Phase B).

The results of the Phase A single dose interim analysis found that there were no toxicologically relevant changes seen in clinical observations, body weights, clinical chemistry, hematology, coagulation or urinalysis parameters. There were no macroscopic or microscopic findings identified in histology that were considered test article related. The multidose Phase B portion of the study showed no test article-related mortalities or macroscopic findings. No toxicologically relevant differences were seen in clinical observations, body weights, clinical chemistry, hematology, coagulation, or urinalysis parameters. There were incidences of test-article related microscopic findings noted for intranasally treated animals, however, these incidences were scored “minimal” to “mild”. Specifically, intranasally treated rabbits showed increased incidences and/or severity of mixed cell inflammation and increased alveolar macrophages in the lung of low dose and high dose males and females. A complete recovery was observed in male rabbits and partial recovery in female rabbits. Of note, the same effects were observed sporadically in control animals, although at lower severity. This effect may be due to dosing material entering the lungs and may therefore be an indirect effect of the protein drug substance in the lungs, and not a direct effect due to Q-GRFT’s mode of action. Some evidence of systemic immunogenicity was seen with detectable and/or low yet quantifiable amounts of anti-drug antibodies (ADAs) noted in 11 rabbits following the 15-day intranasal or IV Q-GRFT dose treatment and 14-day recovery period. This mild induction of ADA is in contrast to the lack of ADA observed in the 30-day rat exposure study. The results also underpin the sensitivity of the species, with the rabbit model showing higher sensitivity than rat for immunological and other toxicological findings. Based on these findings, the MTD of Q-GRFT is considered equal to or greater than 3 mg API when given intranasally and equal to or greater than 1.29 mg API when given intravenously daily for 15 days. The NOAEL was not observed for intranasal dose treatment and is therefore considered to be less than 1.5 mg API when given intranasally once a day for 15 days. The NOAEL for intravenous administration was greater than 1.29 mg API when given once daily for 15 days.

Study M494-21 was a five day repeat dose eye irritation study Q-GRFT intranasal dose formulation in New Zealand White Rabbits. The objective of this study was to determine the ocular irritation potential of Q-GRFT, formulated for intranasal delivery, after once daily single ocular (topical drops) treatment at 0.75 or 1.5 mg administered to the right eye, or twice daily (BID) treatment at 1.5 mg to the right eye (total dose of 3 mg/day) administered for 5 consecutive days to New Zealand White rabbits. Control Group 1 received twice daily administration of the control vehicle to the right eye. The left eye served as the untreated control eye for each animal. Three male and female rabbits were assigned to each treatment group. The human dose is 3 mg/ intranasal administration and hence the BID animals received the full human clinical dose daily for 5 consecutive days.

No animal morbidities or deaths occurred. Clinical observations conducted once daily post-dose showed that all animals appeared normal with no adverse findings. No statistically significant

changes in group mean body weight was observed compared with controls and all animals maintained or gained weight over the course of the study.

No adverse ocular effects were observed following once daily administration of Q GRFT at 0.75 or 1.5 mg once daily, or twice daily administration of 1.5 mg (3 mg total) for 5 consecutive days. Because no adverse ocular effects were observed, the MTD of Q GRFT cannot be determined but is considered to be at least 3 mg (1.5 mg twice daily).

Study G529-21 evaluated the effect of Q-GRFT on mouse bone marrow to rule out potential genetic toxicity caused by exposure to Q-GRFT API. The objective of this study was to evaluate the capacity of Q-GRFT to induce chromosomal or mitotic spindle abnormalities in bone marrow cells of treated mice, as indicated by an increased incidence of micronuclei in newly formed, RNA-containing erythrocytes (polychromatic erythrocytes, PCE). Male and female Swiss Webster mice (Mus musculus) 6-8 weeks of age were the test species (5M/5F per group). Doses ranged from 0 to 20 mg/kg Q-GRFT; the highest dose equated to 465-times Human Equivalent Dose (20 mg/kg mouse/0.043 mg/kg human) if the 3 mg of clinically administered drug (IN) were to be totally absorbed. The animals were administered Q GRFT PBS solution or PBS vehicle control solution intravenously on Day 1, or urethane positive control solution by oral gavage, via a single administration of test article on Day 1. Mortality and morbidity were observed twice daily and clinical observations once daily. Body weights were measured at pre-dose for the purpose of dose calculation. Necropsies were on Days 2 and 3. Q-GRFT was judged to be negative for the induction of micronuclei under the test conditions used in the mouse bone marrow micronucleus assay. By this assay, Q-GRFT is not genotoxic.

Clinical Safety

Q-GRFT has been tested in two clinical studies as part of development for a separate indication (prevention of HIV infection). The PREVENT HIV rectal microbicide Phase 1 study was initiated in 2019 at the University of Pittsburgh. The study is entitled: “A Randomized, Double-Blind Phase 1 Safety and Pharmacokinetic Study of Q-Griffithsin Enema Administered Rectally to HIV-1 Seronegative Adults” (NCT04032717). The purpose of this first in human (FIH) Phase 1 clinical study was to assess the safety, tolerability, and acceptability of a single dose of Q-GRFT enema in healthy adult participants (aged 18-45 years), practicing receptive anal intercourse (RAI). Study participants were topically administered a single rectal dose of study product consisting of either 40 mg of Q-GRFT in a 125 ml saline enema or a 125 mL saline placebo. The study enrolled 21 participants, with 15 participants receiving the Q-GRFT enema. To date, the study has reported three mild (Grade 2 or lower) AEs with all lab values being within reference ranges. Q-GRFT was not detectable in plasma after administration in any participant. Although preliminary, the findings of this FIH study of mucosally administered Q-GRFT antiviral lectin are reassuring from the standpoint of safety and tolerability.

GRFT has also been investigated by the Population Council (www.popcouncil.org) as a potential HIV prophylactic. In a FIH study in 15 female volunteers, griffithsin/carrageenan gel administered vaginally for up to 14 days was found to have a favorable safety profile, and no GRFT was detected in plasma samples. The results of this study have not yet been published but were presented at the HIV R4P conference in October 2018[5].

2.5 PK Data: Q-GRFT

Intranasal administration of Q-GRFT to rats and rabbits indicated low levels of Q-GRFT reach systemic circulation with this route of administration. In a rat PK/BA study of Q-GRFT, very low levels of systemic exposure were observed after QD and BID intranasal administration, with highest plasma level of 14.44 ng/mL, which corresponds to an estimated 0.15% of dose administered In a 30 day multi-dose study, rats with once daily or twice daily intranasal administration, low levels of Q-GRFT in plasma (1.02 – 21.6 ng/mL) were detected in some animals up to 14 hours post-dose. Single day intranasal administration of Q-GRFT nasal solution (same as clinical formulation) to rabbits showed mean apparent Cmax of 17.1 ng/ml (male) at a

dose of 1.5 mg and 137 ng/ml (males) and 63.2 ng/ml (females) at the 3 mg dose. Q-GRFT was eliminated with a mean terminal t1/2 of 15.8 hr (males) and 18.8 hr (females) in the 3 mg intranasal group. Repeated daily intranasal administration of Q-GRFT nasal solution to rabbits for 15 days showed that the mean apparent Cmax on Day 15 was 61.7 ng/ml (female) at a dose of 1.5 mg, and 63.3 ng/ml (males) and 147 ng/ml (females) at a dose of 3 mg. Plasma exposure to Q-GRFT was 2.5-fold greater with the BID regimen versus the QD regimen in the intranasal groups on Day 15, based on AUC_{last} values. The mean AUC_{last} was 1,866 hr*ng/ml in 3 mg dosed females and 733 hr*ng/ml in 1.5 mg dosed females on Day 15. The bioavailability of intranasal Q-GRFT is 0.1% in Phase B after repeated administrations, and therefore, accumulation is unlikely to be an issue in human studies. A slight (~2x single exposure), increase in exposure was seen with repeat dose intranasal (3 mg dose), however, this increase was statistically non-significant (P>0.05) and observed in only few animals.

Results of a single-administration PK/BA study showed that the average t1/2 of Q-GRFT DS delivered intravenously (IV) in male and female Sprague-Dawley rats is 6-7 hours (Study B949-17; see IND 130697). Single dose of IV administered Q-GRFT in male and female rabbits also showed a similar terminal t1/2 of 7.7-9.4 h. Whereas, 15-day daily IV administration of Q-GRFT had a mean terminal t1/2 of 29.0 h in males and 26.0 h in females after IV administration on Day 15 and was longer than that observed on Day 1 of single dose study. Although not evaluated in same animals, repeat dose administration of Q-GRFT for 15 days seems to have resulted in Q-GRFT accumulation in plasma. The mean AUC_{last} on Day 15 (74,825 h*ng/ml in males and 96,992 h*ng/ml in females) was over 5-fold greater than the mean AUC_{last} on Day 1 (13,454 h*ng/ml in males and 17,329 h*ng/ml in females) in IV Group 5 (1.29 mg Q-GRFT). The accumulation of Q-GRFT on Day 15 in the IV group might be due to a saturation of metabolism and/or elimination pathways of the API. Q-GRFT was not bioavailable intrarectally at either the 0.3% (2.5 mg/kg) or 3.0% (25 mg/kg) Q-GRFT formulations. The amount of Q-GRFT to be applied intranasally is significantly less than the rectal dose and Q-GRFT is not expected to be systemically absorbed in significant levels from the nasal application.

Similarly, analyses of rat and rabbit sera from animals administered Q-GRFT carbopol formulations in GLP-compliant studies (21-day repeat-dose plus 14-day recovery, Studies M333-17 and M334-17) showed no Q-GRFT in any of the samples. These results demonstrated that neither Q-GRFT DS nor gel-formulated DP are absorbed systemically when delivered intrarectally to rats and rabbits for up to 21-consecutive days at doses up to 3% API.

In PREVENT HIV, the Phase 1 study examining safety and tolerability of rectal administration of Q-GRFT, Q-GRFT was not detectable in plasma after administration in any participant.

The length of time that Q-GRFT persists in the nasal mucosa after intranasal administration in humans is currently not known and will be examined in this trial. Based on in vivo studies in rats and rabbits, intranasal administration of Q-GRFT may result in low levels of systemic exposure.

2.6 Summary

Q-GRFT has demonstrated excellent safety in prior in vitro and ex vivo tissue studies, in vivo animal studies in three species and preliminarily in human rectal studies. Although there are differences between the rectal and nasal mucosae, there are also similarities, and we believe that much of the nonclinical information generated for topical microbicide should translate and inform the development and use of the nasal formulation. Mucosal surface area exposure in the proposed Phase 1 study is lower by a factor of 6-7 than previous studies. These results are sufficient to initiate a Phase 1 study for intranasal application of Q-GRFT spray as a prophylactic for SARS-CoV-2. The successful completion of this study will inform decisions about whether nasal administration of Q-GRFT is safe.

3 OBJECTIVES

3.1 Primary Objective:

- To assess the local and systemic safety of intranasal Q-GRFT after 14 doses

3.2 Primary Endpoint:

- The proportion of participants who experience a related Grade 2 or higher adverse event

3.3 Secondary Objectives:

- Persistence: To determine the persistence of Q-GRFT in the respiratory tract after a single dose and after 13 days of daily use as assessed by nasopharyngeal swab
- Pharmacokinetics: To determine the systemic absorption of Q-GRFT after administration of a single dose and after 13 days of daily use
- Acceptability: To assess the acceptability of a Q-GRFT nasal spray

3.4 Secondary Endpoints:

- Persistence: Q-GRFT concentrations from nasopharyngeal swabs collected 24 hours after a single dose and 24 hours after 13 consecutive daily doses
- Pharmacokinetics: Q-GRFT concentrations in plasma 24 hours after the first dose and 24 hours after the 13th consecutive daily dose
- Acceptability: Self-reported assessment of qualities of the experience with the nasal spray through a Likert scoring of acceptability questions

3.5 Exploratory Objectives:

- To assess the impact of Q-GRFT nasal spray on smell
- Persistence: Q-GRFT concentrations from oropharyngeal and nares swabs collected 24 hours after a single dose and 24 hours after 13 consecutive daily doses
- Presence of Q-GRFT in the gastrointestinal tract after 13 days of consecutive use
- Determine the potential of the Q-GRFT study drug product to induce an immune response by measuring the generation of anti-drug antibodies (ADAs) in plasma/blood samples after multiple Q-GRFT intranasal spray treatments

3.6 Exploratory Endpoints:

- Change in Brief Smell Identification Test (BSIT) score after 13 days of consecutive daily doses compared to baseline
- Persistence: Q-GRFT concentrations from oropharyngeal and nares swabs collected 24 hours after first dose and 24 hours after the 13th consecutive daily dose
- Presence: Q-GRFT concentrations from rectal swab collected 24 hours after the 13th consecutive daily dose
- Immunogenicity of Q-GRFT study product delivered by an intranasal spray system
- Humoral antibody responses to Q-GRFT in plasma/blood by ELISA

4 STUDY DESIGN

4.1 Identification of Study Design

This is a phase I randomized, placebo-controlled, single site safety study

4.2 Summary of Major Endpoints

The proportion of participants who experience a related Grade 2 or higher adverse event.

4.3 Description of Study Population

The study population will be people who meet criteria outlined in Section 5.

4.4 Time to Complete Accrual

Accrual is expected to be completed in approximately 6 months.

4.5 Study Groups

Participants will be randomized 2:1 to Q-GRFT or placebo intranasal spray.

4.6 Expected Duration of Participation

The duration of study participation is expected to be approximately 6-8 weeks. This includes the screening period.

4.7 Site

There is a single study site: UPMC Magee-Womens Hospital, Pittsburgh, PA.

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria will be utilized to ensure the appropriate selection of study participants.

5.2 Recruitment

Participants will be recruited using a combination of outreach for instance through research registries at the University of Pittsburgh, use of IRB approved informational flyers and posters, and through outreach in the areas and clinics of UPMC Magee-Womens Hospital. This combination of recruitment strategies has proven to successfully provide an adequate number of eligible participants for a wide range of studies evaluating investigational products. The study team includes research staff members who can provide potential study participants with a concise synopsis of the study objectives and rationale. If potential participants contact the study office by telephone, text or email, the study staff will review the study objectives and review the inclusion and exclusion criteria with the potential participants utilizing an IRB approved script.

5.3 Retention

Retention of study participants is a high priority and retention of participants in other phase 1 studies of investigational products has been high (>95%) within our research group. This is accomplished through the development of strong locator information including alternative contacts including friends and family members, telephone reminders prior to study visits and the development of rapport with participants.

5.4 Inclusion Criteria

Participants must meet all the following criteria to be eligible for inclusion in the study:

1) Age 18-55
2) Willing and able to provide written informed consent
3) In general good health as determined by the site clinician
4) Willing to have SARS-CoV-2 test performed at screening

   Note regarding positive SARS-CoV-2 test result at screening visit:

   Positive result and asymptomatic: participants may enroll 14 days after a positive test result if they remain asymptomatic

   Positive test result and is/becomes symptomatic: participants may enroll 14 days after the start of

symptoms or positive results (whichever occurred later) as long as afebrile for 24 hours

5) Fully vaccinated for SARS-CoV-2 (does not include booster vaccination)
6) Agree to abstain from any other investigational drug studies for the duration of the study
7) Agree to abstain from nasally administered products, including over-the-counter products, for the duration of the study
8) Report use of an effective method of contraception at enrollment and intending to continue use of an effective method for the duration of study participation. Acceptable methods include:

    a) Males: Male condoms, sterilization of participant or partner, partner use of hormonal contraception or intrauterine device [IUD], identifies as a man who has sex with men exclusively, and/or sexually abstinent for the past 60 days and agrees to remain abstinent for the study duration

    b) Females: Hormonal methods at the time of enrollment, IUD inserted prior to enrollment, sterilization of participant or partner, consistent condom use of male partner for at least 28 days (reports using condoms 10 times in the last 10 acts of intercourse), identifies as a woman who has sex with women exclusively, and/or sexually abstinent for the past 60 days and agrees to remain abstinent for the study duration.

NOTE: Male and Female refer to Sex at Birth, not self-identified gender.
Sexually abstinent refers to penile-vaginal intercourse only.

9) Agree to participate in all study-related assessments and procedures

5.5 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study:

1) Abnormal nasal or throat exam at enrollment
2) If female, pregnancy, or within 42 days of last pregnancy at screening
3) If female, breastfeeding
4) Diagnosed with SARS-CoV-2 in the past 42 days prior to screening
5) Diagnosed or suspected respiratory tract infection in the past 14 days prior to screening
6) Participation in an investigational drug study in past 30 days at screening
7) Any condition that, in the opinion of the Investigator would preclude provision of consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives
8) Use of any intranasal product in the 14 days prior to enrollment
9) Surgical procedure involving the nose or throat 90 days prior to enrollment
10) Any of the following laboratory abnormalities at screening:
    a.) Hgb < 12g/dL (men) and < 11g/dL (women)
    b.) Serum creatinine > 1.1 x ULN
    c.) ALT, AST, and total bilirubin > 1.1 x ULN
11) Grade 2 or higher seasonal allergies at the time of enrollment
12) Reported use of illicit drugs
    a. Non-therapeutic injection drug use in the 12 months prior to screening
    b. Any use of methamphetamine, gamma hydroxybutyrate, cocaine or heroin in the 12 months prior to screening
13) Use of systemic prescription immunomodulatory medications within the 4 weeks prior to the enrollment

6 STUDY PRODUCTS

6.1 Regimen

Each participant will receive a total of 14 doses of intranasal Q-GRFT. A dose consists of two sprays into each naris (400 µL total).

6.2 Administration

To ensure appropriate placement, the clinician will administer the study product for the first application. Participants will be instructed on the proper use of the applicator and have an opportunity to practice spraying into a paper towel. Thereafter, participants will administer the product themselves.

6.3 Study Product Formulation

Griffithsin (GRFT) is a non-glycosylated protein consisting of 121 amino acids. The API to be used in this trial contains a single amino acid substitution, M78Q variant, that is resistant to oxidation yet maintains the parent molecule's pharmacological profile[6]. The drug product is a mixture of Q-GRFT API and excipients at a final concentration of 7.5 mg/mL. The Q-GRFT API used for drug product manufacture is available as a suspension in PBS at 10±2 mg/mL. The final drug product is filled into metered pump nasal spray applicator, Aptar VP7 screw-on actuator fitted to an SGD Type 1 Glass Amber U-Save bottle (fill volume not less than 5.5 mL), for intranasal administration. A matched vehicle solution is also manufactured and dispensed in same applicators. The device requires 5 sprays for priming before first time use and no priming required thereafter for subsequent administrations. Both placebo and DP should be stored at 2-8°C. The placebo and drug product are manufactured in the Rohan Pharmaceutics Laboratories with CBR International serving as the Quality Assurance as per the regulatory requirements for phase 1 products. Additional details regarding study product may be found in the study specific pharmacy manual.

6.4 Study Product Supply and Accountability

cGMP Q-GRFT and placebo nasal spray bottles will be sent to the Magee-Womens Hospital Investigational Pharmacy, and stored at 2-8°C.

The Magee research pharmacist will maintain complete accountability records of all study products received for this protocol and provided to participants. Additional documentation will be required for study product returns, destruction (if applicable). Unused (once dispensed) study products will be handled according to the study specific pharmacy manual.

6.5 Study Product Provision

Study product will be provided to clinic staff only upon receipt of a written prescription signed by an authorized prescriber. Once the nasal spray bottles are dispensed from the pharmacy and provided to the participant, the bottles can be stored at room temperature.

6.6 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation except immunomodulating drugs and intranasal products as detailed below. All concomitant medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations will be recorded on the concomitant medications log form.

All participants will be counseled to avoid the use of intranasal products. Prohibited non-study intranasal products include, but are not limited to, decongestants, saline, steroid, and antihistamine sprays. Participant use of prohibited medications will be documented.

7 STUDY PROCEDURES

This section describes visit-specific study procedures.

7.1 Pre-Screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants (e.g. via telephone using an IRB approved screening script). During these interactions, study staff may explain the study to participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. If the participant is eligible based on a screening script the person's name and appointment time will be placed on the script. If the person signs consent, the telephone script will then become part of the research record. If the person does not sign consent, the form will be de-identified.

7.2 Visit 1: Screening Visit

At the Screening Visit, participants will provide written informed consent prior to study procedures. Study personnel will collect participant locator Information, demographic, and medical history information. The participants will undergo a physical examination including a visual examination of the nose and throat using a lighted instrument (otoscope). Safety labs will be obtained, and for female participants of child-bearing potential, a urine pregnancy test will be performed. A nasopharyngeal swab will be collected for SARS-CoV-2 testing per local standards. Participants who meet all eligibility criteria will be scheduled for the enrollment visit (Visit 2) within 60 days of the screening visit.

The table below outlines the procedures to take place at the Screening visit.

Table 1: Visit 1 Procedures

VISIT 1: SCREENING VISIT	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Written Informed Consent • Informed Consent Comprehension • Assign Study Number (PTID) • Review Eligibility • Collect Contact Information • Medical History and Concomitant Medications • Visit Questionnaire • Provide Available Screening Results • Protocol Counseling • Schedule Next Study Visit, prn • Participant Reimbursement
NASOPHARYNGEAL	• SARS-CoV-2
URINE	• Pregnancy test for participants of childbearing potential
BLOOD	• CBC with platelets • ALT, AST • Creatinine • Total Bilirubin
PHYSICAL EXAM	• Full Physical Exam • Vital Signs (BP) • Height & Weight

7.3 Visit 2: Enrollment

Subjects who meet the inclusion and exclusion criteria following the Screening visit may schedule an Enrollment visit. This visit is to occur within 60 days of the Screening Visit.

At this visit, locator information will be updated, and eligibility reviewed. Participants will undergo a smell assessment prior to drug delivery. The Brief Smell Identification Test (BSIT) contains 12 odorants embedded on scent strips and released when scratched with a pencil tip. The BIST is a forced choice test as participants are instructed to identify an odorant even if no smell is perceived. The total olfaction score using the BSIT is defined as the number of odorants that are correctly identified.

The participant will be sequence randomized to receive either Q-GRFT nasal spray or placebo nasal spray. The clinician will administer the first dose of study product. After reviewing administration instructions, the participant will try the metered dose delivery system by delivering product into a paper towel. Participants will be asked to wait at the research trial site for one hour after product administration for observation. All participants will undergo an assessment of adverse events, targeted physical exam, blood draw, and assessment of smell approximately one-hour postnasal spray administration.

Interested participants may participate in an optional enrollment visit sampling (nasal, oropharyngeal, and nasopharyngeal) at a single timepoint between 1- and 12-hours post product administration. Participants must agree to all three sample collections to be eligible for this optional enrollment visit sampling.

Table 2: Visit 2 Procedures

VISIT 2: ENROLLMENT – PRE	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Review/Confirm Eligibility • Collect/Update Contact Information • Visit Questionnaire • Quality of Life Survey • Update Medical History and Concomitant Medications • Provide Available Screening Results • Protocol Counseling
URINE	• Pregnancy Test (participants of childbearing potential)
PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Smell (BSIT) • Vital Signs (BP)
BLOOD	• Q-GRFT level • ADA test for Anti Q-GRFT antibodies
NASAL	• Q-GRFT level
OROPHARYNGEAL	• Q-GRFT level
NASOPHARYNGEAL	• Q-GRFT level
STUDY PRODUCT	• Randomized to study product • Study Product Provision • Clinician-administered
1-HR POST-DOSE	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Assess/Document Adverse Events • Schedule Next Study Visit • Participant Reimbursement
BLOOD	• Q-GRFT level • CBC with platelets • ALT, AST • Creatinine • Total Bilirubin

PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Smell (BSIT) • Vital Signs (BP)
OPTIONAL SINGLE TIME POINT SAMPLES (1 – 12-hour post-dose)	
Component	**Procedure/Analysis**
NASAL	• Q-GRFT level
OROPHARYNGEAL	• Q-GRFT level
NASOPHARYNGEAL	• Q-GRFT level

7.4 Visit 3 Follow-Up Visit

Visit 3 will occur the day after the enrollment visit. Every effort will be made to time the study visit for 24 hours after dosing. At this visit, a safety assessment will be performed via medical interview, targeted physical exam, and repeat blood tests. An assessment of participant smell will be performed using the BSIT. Samples (blood, nasal, oropharyngeal, and nasopharyngeal) will be collected, and an acceptability questionnaire will be administered.

Table 3: Visit 3 Follow-up Visit Procedures

VISIT 3 FOLLOW-UP VISIT	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Collect/Update Contact Information • Visit Questionnaire • Update Medical History and Concomitant Medications • Protocol Counseling • Assess/Document Adverse Events • Schedule Next Study Visit • Participant Reimbursement
ACCEPTABILITY	• Acceptability Questionnaire
BLOOD	• Q-GRFT level • CBC with platelets • AST, ALT • Creatinine • Total Bilirubin
NASAL	• Q-GRFT level
OROPHARYNGEAL	• Q-GRFT level
NASOPHARYNGEAL	• Q-GRFT level
PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Smell (BSIT) • Vital Signs (BP)

7.5 Visit 4 [Extended Dosing; 1st week of study product provision]

Visit 4 will occur 5-49 days after Visit 3. If any of the safety labs (e.g.Hemoglobin, AST, ALT, Creatinine, bilirubin) obtained at Visit 3 are returned as Grade 2 or higher, this visit will be postponed until the abnormal lab returns to Grade 1 or Grade 0 but within the 49-day window period.

Ideally, participants will return within the week for Visit 4 but the extended window will allow for flexibility for the participant or any disruptions to visit scheduling caused by external forces, for example a spike in SARS-CoV-2 cases at the institution prompting a pause in study visits. Medical history will be updated, a targeted physical exam conducted, safety labs, blood and respiratory sampling obtained, and study product provided to the participant. After reviewing administration instructions with the participant, the first dose of the 13-day course will be self-administered under direct observation in the clinic. The participant will then self-administer product daily at home for the remainder of the dosing period. A one-week supply will be provided at Visit 4.

Participants will be provided with an administration log to record date and time of drug

administration.

Table 4: Visit 4 Follow-up Visit Procedures

VISIT 4 FOLLOW-UP VISIT [week one of extended dosing]	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Collect/Update Contact Information • Visit Questionnaire • Quality of Life Survey (pre-dose) • Update Medical History and Concomitant Medications • Protocol Counseling • Provision of Study Product (week one supply) • Assess/Document Adverse Events • Schedule Next Study Visit • Participant Reimbursement
BLOOD	• Q-GRFT level • CBC with platelets • AST, ALT • Creatinine • Total Bilirubin
URINE	• Pregnancy test (participants of childbearing potential)
OROPHARYNGEAL	• Q-GRFT level
NASAL	• Q-GRFT level
NASOPHARYNGEAL	• Q-GRFT level
PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Smell (BSIT) • Vital Signs (BP)

Participants will be contacted in between Visit 4 and Visit 5 to assess for adverse events. This contact will be considered Visit 4a.

7.6 Visit 5 [Extended dosing; second week of product provision)

Visit 5 will occur 7 days after Visit 4. A safety assessment will be performed via medical interview and physical exam. An assessment of smell will be performed. The second week of study product will be provided. Participants will be provided with an administration log to record date and time of drug administration.

Table 5: Visit 5 Follow-up Visit Procedures

VISIT 5 FOLLOW-UP VISIT [week two of extended dosing]	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Collect/Update Contact Information • Visit Questionnaire • Quality of Life Survey • Update Medical History and Concomitant Medications • Protocol Counseling • Assess/Document Adverse Events • Provision of Study Product (week two supply) • Schedule Next Study Visit • Participant Reimbursement
PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Smell (BSIT) • Vital Signs (BP)
BLOOD	• CBC with platelets • AST, ALT • Creatinine • Total Bilirubin

Participants will be contacted in between Visit 5 and Visit 6 to assess for adverse events. This contact will be considered visit 5a.

7.7 Visit 6

Visit 6 will occur approximately 13 days after Visit 4. Every effort will be made to time the study visit for 24 hours after the last self-administered dose. At this visit, a safety assessment will be performed via medical interview, targeted physical exam, and repeat blood tests. An assessment of participant smell will be performed using the BSIT. Blood and respiratory samples will be collected. An acceptability questionnaire will be administered. Participants have the option to have a rectal swab collected.

Table 6: Visit 6 Follow-up Visit Procedures

VISIT 6 FOLLOW-UP VISIT [24 hours after last self-administered dose]	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Collect/Update Contact Information • Visit Questionnaire • Quality of Life Survey • Update Medical History and Concomitant Medications • Protocol Counseling • Assess/Document Adverse Events • Schedule Next Study Visit • Participant Reimbursement
BLOOD	• Q-GRFT level • ADA test for Anti Q-GRFT antibodies • CBC with platelets • AST, ALT • Creatinine • Total Bilirubin
ACCEPTABILITY	• Acceptability Questionnaire
URINE	• Pregnancy test (participants of childbearing potential)
NASAL	• Q-GRFT level
OROPHARYNGEAL	• Q-GRFT level
NASOPHARYNGEAL	• Q-GRFT level
RECTAL (optional)	• Q-GRFT level
PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Smell (BSIT) • Vital Signs (BP)

7.8 Visit 7

Visit 7 will occur 28 days after Visit 4. At this visit, a final safety assessment will be performed via medical interview, targeted physical exam, and repeat blood tests. An assessment of participant smell will be performed using the BSIT. Samples (blood and respiratory) will be collected. An acceptability questionnaire will be administered.

Table 7: Visit 7 Follow-up Visit Procedures

VISIT 7 FOLLOW-UP VISIT	
Component	**Procedure/Analysis**
ADMINISTRATIVE	• Visit Questionnaire • Quality of Life Survey • Update Medical History and Concomitant Medications • Assess/Document Adverse Events • Participant Reimbursement
ACCEPTABILITY	• Acceptability Questionnaire
BLOOD	• Q-GRFT level • ADA test for Anti Q-GRFT antibodies • CBC with platelets • AST, ALT • Creatinine • Total Bilirubin
URINE	• Pregnancy test (participants of childbearing potential)
NASAL	• Q-GRFT level
OROPHARYNGEAL	• Q-GRFT level
NASOPHARYNGEAL	• Q-GRFT level
PHYSICAL EXAM	• Targeted Physical Exam • Assessment of Taste and Smell (BSIT) • Vital Signs (BP)

7.9 Visit Window Periods

While every attempt will be made to evaluate the participant on the protocol specified date, the following visit windows are allowable

Visit 3: 24 hours after first dose (24-48 hours)
Visit 4: 5-49 days after Visit 3
Visit 5: 7 days after Visit 4 (5-7 days)
Visit 6: 13 days after Visit 4 (12-13 days) *
Visit 7: 28 days after Visit 4 (25-32 days)

*If scheduling requires that the participant be seen 12 days after Visit 4 rather than 13 days after, participants will be instructed to hold the final home dose and present to the clinic the next day

7.10 Participants Who Become Pregnant

Urine pregnancy tests will be performed at screening, enrollment Visit 4, Visit 6, and Visit 7 for participants of pregnancy potential. Participants who become pregnant will be referred for care. Participants will remain in the study for safety but study product will be discontinued, if applicable . Pregnant participants will be contacted after their study participation to ascertain the pregnancy outcome.

7.11 Interim Visits

Interim visits may be performed at any time during the study (and study procedures repeated as clinically indicated), for the following or other reasons:

- In between screening and enrollment or Visits 3 and 4 if laboratory tests need to be repeated due to out of range values

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care.
- In the event of laboratory processing issues (i.e., lost or inadequate sample)
- For other reasons at participant request.

Details of the interim visit will be recorded in the chart notes.

7.12 Clinical Evaluations and Procedures

Physical exams will include the following assessments.

A targeted physical exam will include:

- Vital signs:
  - Blood pressure

- Measurements of:
  - Weight (at Screening only)
  - Height (at Screening only)

- Visual assessment of nose and throat

A full physical exam will include the components of the targeted exam as well as the following:

- General appearance
- Cardiac exam
- Respiratory exam
- Abdomen

Additional assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

7.13 Laboratory Evaluations

Urine pregnancy test
Clinical and Translational Research Center
University of Pittsburgh Medical Center
300 Halket Street Room 5521
Pittsburgh, PA 15213

CBC with platelets, AST, ALT, Creatinine, Total Bilirubin, SARS-CoV-2 testing
UPMC Presbyterian Shadyside CP PUH
UPMC Clinical Laboratory Building 3477
Euler Way
Pittsburgh, PA 15213

Q-GRFT levels in blood, nasal, oropharyngeal, nasopharyngeal, and rectal samples and anti-Q-GRFT antibodies
Matoba Laboratory, University of Louisville, Owensboro Cancer Research Program

7.14 Specimen Collection and Processing

The site will adhere to the standards of good clinical laboratory practice and site standard operating procedures for proper collection, processing, labeling, handling, transport, and storage of specimens. In cases where laboratory results are not available due to administrative or laboratory error, study staff is permitted to re-draw and/or re-collect specimens.

7.15 Biohazard Containment

As the transmission of SARS-CoV-2 can occur through contact with an asymptomatic infected individual, site staff will use appropriate personnel protective equipment per Centers for Disease Control guidance. As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY AND CLINICAL MANAGEMENT

8.1 Safety Monitoring

The study site investigator is responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Chair if unexpected concerns arise.

8.2 Clinical Data Safety Review

Appropriate safety monitoring will be contingent upon excellent communication between study participants and study staff. Data collected from participants will include changes in medical status, concomitant medications and side effects. All adverse events will be reported as outlined in the study protocol and will be monitored by the study staff, investigators, and an Independent Safety Monitor on a regular basis. Any immediate safety concerns will be brought to the attention of the Principal Investigator. Adverse events will be reported to the IRB as required by IRB guidelines.

An Independent Safety Monitor who is familiar with the pertinent scientific literature related to intranasal medications and potential side effects will be responsible for safety monitoring. This individual will be a physician independent of the study sponsor and the principal investigators and will be available to monitor data from this single site. The Independent Safety Monitor will evaluate adverse event data on a routine basis to determine whether the study protocol should continue as originally designed, should be changed, or should be terminated. Any change to the anticipated benefit-to-risk ratio identified will be reported to the IRB. In addition, any breaches of confidentiality will be reported for review.

8.3 Adverse Events Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the study product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whetheror not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

SAEs will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the above

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation at UPMC Magee-Womens Hospital, where the study clinicians are based, and to request that a study clinician be contacted upon their arrival. All participants reporting a clinically significant untoward medical occurrence will be followed either in person or by phone until the occurrence resolves (returns to baseline) or stabilizes over a four-week period.

For each study participant, AE documentation and reporting will be undertaken throughout the scheduled duration of follow-up.

The Protocol chair/designee will grade the severity of each AE and the relationship of the AE to study product:

AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1, July 2017

It is anticipated that most AEs will not be specifically identified in the DAIDS toxicity table and will be graded by the Estimating Severity Grade for Parameters Not Identified in the Grading Table row of the toxicity table.

Table 8: DAIDS toxicity table

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Relatedness is an assessment made by a study clinician of whether the event is related to the study agent. Degrees of relatedness will be categorized according to current DAIDS-approved guidelines. Per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), the relationship categories that will be used for this study are:
- *Related:* There is a reasonable possibility that the AE may be related to the study agent(s)
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent(s)

All AEs will be captured through REDCap on an AE log form. The form should be reviewed at each study visit and updated as needed. For any serious AEs (SAEs) that are continuing at a participant's study exit visit, the Protocol chair or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff at least 2 weeks after the participant's study exit visit; additional evaluations also may take place at the discretion of the PI/designee. The same approach must be taken for any AEs deemed related to study product that are found to have increased in severity at the study exit visit. For those AEs requiring re- assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date.

8.4 Clinical Management of Adverse Events

By definition, an adverse event can be either new finding or symptom or a worsening of a pre-existing condition. In order to accurately capture adverse events in follow-up, a thorough baseline history will be obtained at Visit 1. For example, for participants who endorse a history of headache, site staff will probe for and record details surrounding the condition such as frequency, location, duration, medication use, triggers, etc. Only by eliciting a full description will study staff be equipped to determine whether a subsequent event in follow-up is a clinically distinct event or not.

Adverse events will be elicited at each follow-up visit. Referral to appropriate care will be offered to participants as needed.

Any Grade 3 AE's that are deemed to be related to the study product will be reviewed within 5 days by an ENT investigator. The ENT investigator and the PI will determine whether the participant will continue in the study.

If a participant experiences a Grade 4 AE related to the study product or any SAE related to the study product, the study product will be held. The AE will be reviewed by the ENT investigator within 3 days. They will be discontinued from the study and followed for safety and outcome of the event.

8.5 Product Removal

In the unlikely event that a participant is intolerant of the study product immediately after placement, the site clinician will remove any residual drug with a sterile saline wash and a moistened swab if necessary.

8.6 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The Site PI/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, including the Office of Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

9 STATISTICAL CONSIDERATIONS

9.1 Review of Study Design

This is a first in human multi-day dose phase 1 randomized, double-blind, placebo-controlled study to evaluate safety after 14 doses of Q-GRFT prepared in saline. The primary aim of the study is to assess the local and systemic safety of nasally administered Q-GRFT in healthy adults. The primary endpoint is the proportion of participants who experience a Grade 2 or higher related adverse event.

9.2 Sample Size and Accrual

Accrual of approximately 45 evaluable participants is expected to take 6 months. The expected duration of study participation for each participant will be approximately 6-8 weeks. This includes the screening period. Participants will be randomized 2:1 (Q-GRFT nasal spray: placebo nasal spray) resulting in 30 participants enrolled into the Q-GRFT arm and 15 participants enrolled into the placebo arm.

The primary aim of the study is to assess the local and systemic safety of nasally administered Q-GRFT in healthy adults. The primary endpoint is the proportion of participants who experience a Grade 2 or higher adverse event deemed related to study product. The proposed total sample size is N=45 divided into 2 arms (Q-GRFT and placebo assigned at a 2:1 ratio). The sample size is based on the exact binomial probability of observing at least two Grade 2 or higher related adverse events in the Q-GRFT arm. Table 1 gives the upper and lower bounds for the 95% exact binomial confidence intervals of the true Grade 2 or higher adverse event rate at all possible numbers of observed events in a group of size 30. Note that the results for more than 50% of events in each group are not listed, but by symmetry can be calculated as 1- the listed rate and 95% CI for the number of non-events. If none of the 30 participants experience Grade 2 or higher adverse events, the 95% exact 2-sided upper confidence bound for the Grade 2 adverse event rate is 11.6%. In a Cochrane review of intranasal steroids for rhinosinusitis, the rate of any adverse event was 5.5%[8]. If similar event rates are observed in the proposed study, we will be able to rule out Grade 2 or higher adverse event rates greater than 22.1% in the Q-GRFT study arm.

Table 9: 95% confidence intervals for the true rate at all possible observed Grade 2 or higher adverse event rates

Number of observed events	Rate (95% CI)
0/30	0 (0, 11.6%)
1/30	3.3% (0.1%, 17.2%)
2/30	6.7% (0.8%, 22.1%)
3/30	10.0% (2.1%, 26.5%)
4/30	13.3% (3.8%, 30.7%)
5/30	16.7% (5.6%, 34.7%)
6/30	20.0% (7.7%, 38.6%)
7/30	23.3% (9.9%, 42.3%)
8/30	26.7% (12.3%, 45.9%)
9/30	30.0% (14.7%, 49.4%)
10/30	33.3% (17.3%, 52.8%)
11/30	36.7% (19.9%, 56.1%)
12/30	40.0% (22.7%, 59.4%)
13/30	43.3% (25.5%, 62.6%)
14/30	46.7% (28.3%, 65.7%)
15/30	50.0% (31.3%, 68.7%)

9.3 Study Endpoints

9.3.1 Primary Endpoint

The proportion of participants who experience a related Grade 2 or higher adverse event.

9.3.2 Secondary Endpoints

Persistence: Q-GRFT concentrations from nasopharyngeal swabs 1) collected 24 hours after a single dose and 2) collected 24 hours after 13 consecutive daily doses

Pharmacokinetics: Q-GRFT concentrations in plasma 1) 24 hours after the first dose and 2) 24 hours after the 13th consecutive daily dose

Acceptability: Self-reported assessment of qualities of the experience with the nasal spray as assessed by acceptability questionnaires. Product attributes considered likely to discourage future use by participants, will be dichotomized as having a rating of lower than 3 on a 5-point Likert scale.

9.3.3 Exploratory Endpoints

Change in Brief Smell Identification Test (BSIT) score after 13 days of consecutive daily doses compared to baseline

Persistence: Q-GRFT concentrations from oropharyngeal and nares swabs collected 1) 24 hours after first dose and 2) 24 hours after the 13th consecutive daily dose

Presence: Q-GRFT concentrations from rectal swab collected 24 hours after the 13th consecutive daily dose

Immunogenicity of Q-GRFT study product delivered by an intranasal spray system

Humoral antibody responses to Q-GRFT in plasma/blood by ELISA

9.4 Blinding and Unblinding

Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis.

Unblinding may need to be performed on an individual basis for assessment of a serious AE and/or for the safety of the participant. Details of emergency unblinding are specified in an SOP.

9.5 Randomization

The randomization scheme will be generated and maintained by a member of the Data Management Center at Magee-Womens Research Institute and supplied to the Pharmacy at Magee-Womens Hospital. Participants will be randomized to the sequence of the two nasal spray formulations, active or placebo, in a 2:1 ratio using a permuted block design with random block sizes of 3 and 6. To minimize bias in the group assignment, participants will be given study randomization numbers. Participants will be randomized using REDCap's randomization module to obtain the sequence of product assignment. When a participant is ready to be randomized, the study investigator (PI/Co-I) will open the Randomization eCRF in REDCap and confirm that the participant is being enrolled. REDCap will then assign a randomization number which the study investigator (PI/Co-I) will print and take to the pharmacy to obtain the study product indicated by the randomization scheme. The study product will be labeled in order to mask the product assignment to the participants and study staff. The randomization scheme will be created for a total of 48 participants.

9.6 Data Monitoring and Analysis

9.6.1 Data Monitoring

This clinical trial will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements. All paper research charts are maintained in locked files in a locked room. The data management research staff, under the direction of the primary investigator, will create and maintain databases using REDCap (Research Electronic Data Capture) which is a secure, validated, web-based application designed for clinical trial data collection. The databases will be backed up nightly, weekly, and monthly onto the University of Pittsburgh's server's back-up system. Appropriate firewall and virus scanning software are installed and updated routinely by the university support staff.

This study will utilize electronic data capture. Site staff will enter data as collected directly into a data entry system. Study data management staff will review the electronic data elements for completeness and accuracy. If there are any responses that are incomplete, unclear, or inconsistent with related data elements, the staff person will communicate with the clinician in question as soon as possible to resolve the problem. If necessary, the study staff will make the appropriate change in the electronic database which tracks time, date, and by whom a change is made.

9.6.2 Statistical Analysis

The number of adverse events will be summarized by severity, body system, and relationship to study product using frequencies and percent. Individual participants will contribute once to the calculation of event rates. Differences in the prevalence of adverse events between the study arms will be assessed using Fisher's exact test.

Descriptive statistics (frequency, medians, range, means, standard deviation) will be used to summarize the secondary and exploratory endpoints. Differences in Q-GRFT concentration and BSIT score between the study arms will be evaluated using Student's t- or Mann Whitney U tests, where appropriate. Fisher's exact tests will be used to assess differences in the presence of Q-GRFT in the gastrointestinal tract and dichotomized acceptability endpoints between the two study arms. Spearman's correlation coefficients Fisher's exact, and Mann-Whitney U tests may be used in exploratory analyses to evaluate the impact of gender, age and race on the pharmacokinetics and acceptability of the Q-GRFT nasal spray.

9.6.3 Analysis Cohort

The intent-to-treat cohort (ITT) will be defined as those who were enrolled. It will be used for analyses of baseline characteristics, protocol deviations and violations, and trial conduct. The evaluable cohort (Eval) is a subset of ITT participants. Evaluable participants will be defined as participants who complete Visit 6 procedures.

10 HUMAN SUBJECTS CONSIDERATIONS

The investigators will make efforts to minimize risks to human subjects. Volunteers will take part in a thorough informed consent process throughout their participation in the study. Before beginning the study, the investigators will have obtained IRB approval. The investigators will permit audits by the NIH or any of their appointed agents.

10.1 Special Populations

Study staff will offer screening to people of all ethnic and racial groups. Members of the study staff are not seeking the screening or enrollment people in special or vulnerable populations.

Women and Minorities

SARS-CoV-2 uninfected women and men of all races and ethnicities represented at the Magee-Womens Hospital clinical site will be recruited into the clinical protocol. Men and women who provide written informed consent and meet the eligibility criteria will be enrolled. It is anticipated that gender distribution of the 45 study participants will be approximately 60% female (n=27) and approximately 40% male (n=18). While SARS-CoV-2 infects women and men equally, a larger proportion of female participants is anticipated based on the recruitment population available at Magee-Womens Hospital. Allegheny county, the location of Magee-Womens Hospital, has a population of approximately 2.2 million and is comprised of 89% white not Hispanic, 13% black or African American, 2% Hispanic, 4% Asian, 2% mixed race and 0.2% American Indian. The anticipated study population is expected to reflect the distribution of Allegheny County residents, except for Black or African Americans who will be recruited preferentially to comprise at least 20% of the study population since blacks and African Americans are disproportionately impacted by Covid-19. In our past phase 1 studies of investigational products, we have been able to accomplish recruitment of a larger proportion of black and African American study participants through outreach at clinics having high attendance by underrepresented minority patients and through the use of culturally competent and diverse study staff who have developed strong relationships with minority communities in Allegheny County.

Children

This clinical study is not seeking to enroll special or vulnerable populations or children < 18 years of age. This clinical trial will be the first-in-human multi-day dose study of an investigational drug product intended to provide protection from infection by SARS-CoV-2, the virus which causes Covid-19. The study is designed to evaluate the safety of a new product for which the safety profile is not yet defined. Studies conducted in children are generally deferred until such time as the safety of an investigational product has been established in a healthy adult population.

Prisoners

Prisoners will not be included in this study (for screening or enrollment). Any participants incarcerated during participation in the trial will not be followed during their incarceration and will be discontinued from the study.

Pregnant women

Pregnancy is an exclusion criterion as this is a first in human multi-day dose study. Women who become pregnant during the study period following enrollment will not be excluded from analysis. Participants who become pregnant during the study will continue with follow up visits and will be contacted periodically after study completion in order to determine the pregnancy outcome.

10.2 Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. The informed consent process will give individuals all the relevant information they need in order to decide whether to participate, or to continue

participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Only listed study investigators may obtain informed consent from potential study participants. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

Risk/Benefit Statement

Risks

It is not expected that this study will expose healthy participants to unreasonable risk. While this is the first in human multi-day dose assessment of Q-GRFT administered intranasally, Q-GRFT is under evaluation n a Phase I clinical trial as a rectal enema product for HIV prevention at Magee-Womens Research Institute within an NIAID U19 funded collaboration between the University of Pittsburgh and the University of Louisville (U19 AI113182, K. Palmer Program Director). No safety issues have been identified to date in 15 healthy volunteers who have received a single dose enema containing 10mg/mL of Q-GRFT in phosphate buffered saline.

As with any intranasally administered product, nasal congestion, nasal discharge, nasal burning, nasal irritation, increased mucus, nasal dryness, sneezing, coughing, pharyngitis, epistaxis, mucosal erythema, nasal ulceration, interference with taste and smell, tinnitus, and headache are potential risks and participants will be closely monitored for these. Hypersensitivity reactions (including contact dermatitis and rash) are rare risks with any product. As the drug is intended to work at the mucosal surface, systemic side effects are presumed to be exceptionally unlikely. Nonetheless, safety labs including CBC with platelets, AST, ALT, total bilirubin and creatinine will be checked pre and post administration.

A rare but potentially life-threatening risk of exposure to nasal spray containing Q GRFT or the placebo spray would be anaphylaxis. Risk will be mitigated by having the single application of the product in the clinical research site and having people remain in the clinical trial facility for 1 hour after application.

Additional Risks:

Nasal specimen collection may cause mild discomfort and/or nasal spotting. Oropharyngeal swab collection may induce a gag reflex and cause mild discomfort. Nasopharyngeal swabs may cause discomfort, eyes to water, coughing/gagging. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, bruising, swelling and/or infection. Collecting a rectal swab may cause discomfort. Testing positive for SARS-CoV-2 could impact a participant's social and work schedule. Testing positive for pregnancy may cause anxiety.

Potential participants will be screened for SARS-CoV-2 at the screening visit. Anxiety and depression surrounding a positive result is a risk. A positive test result will necessitate that the Allegheny County Health Department be notified; the potential participant will be counselled about this possibility which would likely result in a period of self-quarantine and disruption to his or her daily life.

Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions

Benefits

Participation in these studies may have no direct benefit to volunteers. All volunteers will receive a SARS-CoV-2 test, which some may consider a benefit. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities in blood count, liver or kidney function tests that would have otherwise not been detected. Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of SARS-CoV-2 research. However, there is no guarantee that volunteers will receive any of these benefits.

10.3 Incentives

Volunteers will not be charged for any of the study visits, study supplies or examinations. There are no costs to participants in this study. Pending IRB approval of compensation guidelines, participants will be compensated for their time and inconvenience and for their travel needs while participating in the protocol. The approved amounts of compensation for the time commitment of participants will be given out at each visit. The visits will be pro-rated and partial payment given if the participant only completes a portion of the study visits.

10.4 Participant Confidentiality

Members of the study staff are all trained in patient confidentiality. The log of study subject names and other protected health information is kept in a secure location. All computer information about study volunteers is kept on a computer with log-on passwords. Laboratory specimens are labeled with study numbers and date and are delivered by study staff. In addition to the research study staff, NCI, study monitors, University of Pittsburgh, University of Pittsburgh Office of Research Protections, and/or the University of Pittsburgh IRB may have access to participant's health information. Each member of the staff has log-on identification and password, logs off before leaving a computer screen unattended, and closes their office door when out of the office. All research records will be kept for a minimum of seven years following closure of this study (per University of Pittsburgh policy).

10.5 Communicable Disease Reporting

Study staff members will comply with all local requirements to report communicable diseases including SARS-CoV-2 identified among study participants to the Allegheny County Health Department. Study investigators will include discussion of mandated reporting during the study informed consent process.

10.6 Study Pause/Discontinuation

NCI or the University of Pittsburgh Institutional Review Board may discontinue this study at any time. Ongoing safety monitoring will track the incidence of AEs.

The study will be paused if the following should occur:

- Two or more Grade 3 AEs that are similar in nature and related to study product
- Any Grade 4 AE or SAE related to study product

If the study is paused, the Independent Safety Monitor will evaluate the safety data and recommend whether the study should be discontinued or may be continued with or without a protocol amendment.

11 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

11.1 Laboratory Specimens

Laboratory specimens will be handled in a manner consistent with institutional, OSHA, and GLP guidelines. Study staff members are trained in the appropriate handling of laboratory specimens.

Table 10: Laboratory Test Methods

SAMPLE	METHOD	LABORATORY
URINE	Pregnancy test	Clinical Research Center CLIA #39D1031322
NASOPHARYNGEAL	SARS-CoV-2	UPMC Presbyterian Shadyside CP PUH CLIA# 39D0911193
	Q-GRFT Level	Owensboro Cancer Research Program
BLOOD	CBC with platelets, AST, ALT, Creatinine, Total Bilirubin	UPMC Presbyterian Shadyside CP PUH CLIA# 39D0911193
	Q-GRFT Level	Owensboro Cancer Research Program
	Anti-Q-GRFT Antibody	Owensboro Cancer Research Program
OROPHARYNGEAL, NASAL	Q-GRFT Level	Owensboro Cancer Research Program
RECTAL	Q-GRFT Level	Owensboro Cancer Research Program

11.1.1 Urine Samples

Urine will be tested for HCG via the Sure-Vue® test or equivalent FDA-cleared test.

11.1.2 Respiratory Samples

The assessment of SARS-CoV-2 in the nasopharynx will be assessed by Nucleic Acid Amplification (NAAT) test. Q-GRFT concentrations from nasal, oropharyngeal and nasopharyngeal swabs will be measured according to SOP.

Collection will be done as gently and carefully as possible to collect an adequate sample that is unlikely to disturb the mucosa.

11.1.3 Blood

Q-GRFT concentrations from blood will be measured according to SOP.

11.2 Biohazard Containment

Biohazardous waste will be contained according to institutional and all other applicable regulations.

12 ADMINISTRATIVE PROCEDURES

The study proposal for funding, this protocol, the informed consent document, data collection forms, and advertising flyers are all reviewed by the University of Pittsburgh Institutional Review Board prior to enrollment of participants in the study.

12.1 Protocol Registration

This NIH-funded clinical trial will be registered on ClinicalTrials.gov after the protocol is at version 1 and the submission of the protocol has been completed to the US Food and Drug Administration and to the University of Pittsburgh IRB. Updates of the record on ClinicalTrials.gov will be made to record when the study is open for accrual, when the study has closed to accrual as well as summaries of the results from the study. These updates are accomplished by Dr. Leslie Meyn who heads the Data Management group. Informed consent documents for the clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. The University of Pittsburgh has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements including reminders and updates throughout the year.

12.2 Data Coordination

Data management responsibilities will reside with the Data Management staff at Magee-Womens Research Institute.

12.3 Study Monitoring

The University of Pittsburgh Education and Compliance Office for Human Subject Research (ECO-HSR) will conduct the study monitoring.

The site investigator will make study documents and REDCap as applicable (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspections by the local IRB, the site monitors, the FDA, NCI, the OHRP, and other local and US regulatory entities for confirmation of the study data.

12.4 Protocol Compliance

All protocol amendments will be submitted to and approved by the University of Pittsburgh IRB.

12.5 Investigator's Records

The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. Study records will not be destroyed prior to receiving approval for record destruction from the Principal Investigator and they will be maintained for a minimum of seven years following completion of the study, per the University of Pittsburgh IRB policy. Applicable records include source documents, site registration documents and reports, correspondence, informed consent forms, and notations of all contacts with the participant.

APPENDIX 1 SCHEDULE OF STUDY VISITS AND PROCEDURES

Component	Procedure/Analysis	V1: Screen	V2: Enroll	V3	V4	V5	V6	V7
ADMINISTRATIVE	Written Informed Consent	X						
	Assign Study Number (PTID)		X					
	Review/Confirm Eligibility	X	X					
	Collect/Update Contact Information	X	X	X	X	X	X	X
	Medical Hx/Concomitant Meds	X	X	X	X	X	X	X
	Visit Questionnaire	X	X	X	X	X	X	X
	Quality of Life Survey		X		X	X	X	X
	Provide Screening Results	X	X					
	Protocol counseling	X	X	X	X	X	X	
	Assess/Document Adverse Events		X (post)	X	X	X	X	X
	Schedule Next Study Visit	X	X	X	X	X	X	
	Participant Reimbursement	X	X	X	X	X	X	X
	Safety/AE Assessment Contact				X(V4a)	X (V5a)		
ACCEPTABILITY	Acceptability Questionnaire			X			X	X
NASAL/THROAT	Q-GRFT level		X	X	X		X	X
BLOOD	CBC with Platelets, AST, ALT,Cr, Total Bilirubin	X	X	X	X	X	X	X
	Q-GRFT level		X	X	X		X	X
	Anti-Q-GRFT antibody		X				X	X
NASOPHARYNGEAL	Q-GRFT level		X	X	X		X	X
	SARS-CoV-2	X						
URINE	Pregnancy Test, as applicable	X	X		X		X	X
PHYSICAL EXAM	Physical Exam (full vs. targeted)	X	X	X		X	X	X
	Vital Signs (BP)	X	X	X		X	X	X
	Height & Weight	X						
BSIT	Assessment of Smell		X	X	X	X	X	X
STUDY PRODUCT	Provision of Study Product		X		X	X		

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