APPENDIX II INTERVENTION SPECIFIC APPENDICES

B. INVESTIGATIONAL PRODUCT: USUAL CARE + NITRIC OXIDE NASAL SPRAY

1. INTRODUCTION, RATIONALE AND PROTOCOL STRUCTURE

Given that the nasal passage is often a primary entry point for respiratory infections, and viruses typically replicate in the upper airways prior to infecting lungs, interventions administered intranasally early on in the course of illness could be highly effective in limiting viral spread causing COVID-19 or COVID-like-illness. Nitric oxide nasal spray (NONS) is a nitric oxide (NO) donor that has been found to be effective and safe in reducing viral load and accelerating nasal viral clearance in patients infected with SARS-CoV-2 [1, 2]. NONS targets the virus within the nasal cavity at the point of initial contact, before nasal host cell entry and post-replication release from host cells.

In vitro studies have demonstrated virucidal action of NO against all variants of concern (VOCs) of SARS-CoV-2, and against other respiratory pathogens such as influenza, respiratory syncytial virus (RSV), rhinovirus and other coronaviruses [3]. NO is believed to alter the structural integrity of viral proteins through nitrosylation and palmitoylation reduction; to interfere with the fusion of spike (S) protein to its cognate host receptor angiotensin converting enzyme 2 (ACE-2); and to impede viral protease activity resulting in inhibition of viral RNA replication [4-7]. The inherent low pH (3.5) and virion trapping capacity (hydroxypropylmethylcellulose (HPMC)) of NONS augments the antiviral activity of NO.

Disease severity and risk of COVID-19 progression correlates with the concentration of SARS-CoV-2 virus particles in the upper respiratory tract [8-11]. Moreover, it has been suggested that a shorter time to elimination of viral RNA reduces the time of potential infectivity [9]. NONS works rapidly within the nose to inactivate SARS-CoV-2 to potentially shorten the clinical infection trajectory and virus transmissibility [12, 13].

If effective, NONS could improve recovery outcomes for patients and reduce suffering, result in reduced use of healthcare services, reduce loss of productivity and absence from work, and improve quality of life (physical, mental and social). NONS use is not expected to be associated with the development of drug resistance, or systemic drug-drug interactions.

2. OBJECTIVES

As per master protocol.

3. STUDY DESIGN

3.1 Study Design

This IMP will be tested in a Phase IIb study.

3.2 Study Description

IMP initiation to occur within **3 days** of symptom onset.

3.3 Schematic diagram of study design

As per master protocol.

3.4 Duration of the study per participant

As per master protocol. IMP self-administration for 7 days.

4. STUDY POPULATION

4.1 Population (base)

As per master protocol.

4.2 Inclusion criteria

As per master protocol. Additional inclusion criteria for NONS:

- Onset of symptoms within 3 days.
- For women of child-bearing potential*: prepared to use a highly effective method of contraception or abstinence for 30 days before and after terminating study medication intake.

* See master protocol

4.3 Exclusion criteria

As per master protocol. Additional exclusion criteria for NONS:

- Known to be currently pregnant or breastfeeding. Pregnancy should be ruled out by a negative urine pregnancy test for all women of child-bearing potential* prior to randomisation.
- Current or history of moderate to severe epistaxis or hereditary hemorrhagic telangiectasia.
- History of cerebral spinal fluid leaks via the sinuses/nose.
- Recent nasal fracture, nasal tumors, nasal masses, meningoencephalocele, and/or nasal surgery within the previous 2 weeks.
- Using any of the contradicted agents within 7 days before screening:
    - NO donors/derivatives: isosorbide dinitrate, isosorbide mononitrate, nitroglycerine/glyceryl trinitrate, nitroprusside, nicorandil.
    - Phosphodiesterase inhibitors: avanafil, sildenafil, tadalafil, vardenafil.
    - Guanylate cyclase activators: riociguat, linaclotide.
- Known glucose-6-phosphate-dehydrogenase (G6PD) deficiency.

  * See master protocol

4.4 Sample size calculation

The maximum sample size of 333 per arm has a one-sided error rate less than 2.5% and power around 90% for median time to recovery ranging from 12 to 6 days in the control group and a hazard ratio of 1.33. This assumes analysis using a Bayesian piecewise exponential model with weakly informative priors and interim analyses with early stopping rules for futility and superiority when 150 and 225 patients have been recruited to the control group and have been followed for 28 days. Early stopping rules for both superiority and futility are based on thresholds of the posterior distribution that have been justified using simulation (see M-SAP and section 10 below). Success is declared at maximum sample size if the posterior probability of superiority is greater than a final superiority threshold, which again is specified in the M-SAP and below in section 10.

5. STUDY TREATMENTS

5.1 Investigational Products

5.1.1 Name and description of the IMP

Nitric oxide is a pulmonary vasodilator as is being used via inhalation in clinical practice (in ECRAID-Prime NO is not inhaled but administered intranasally). NONS contains sodium chloride, citric acid, sodium, HPMC, nitrite and benzalkonium chloride. NO is formed during spraying from a dual-chamber device. The dual-chamber device allows mixture of the compounds immediately prior to the coverage of NO. None of the ingredients are considered harmful. NO is a colorless gas with a sharp, sweet odour. NO is a natural molecule and an approved drug created in a liquid formulation.

The IMP is manufactured and supplied by SaNOtize Research and Development Corp. 25th Floor, 700 West Georgia Street, Vancouver, BC, Canada [manufactured at Glenmark Pharmaceuticals Limited Plot No. B-25, MIDC, Shendra Aurangabad 431154 Maharashtra, India]]. Myonex GmbH [Salfuzer 13/14 Aufgang A, 1.OG, 10587 Berlin, Germany] will label and distribute the IMP.

5.1.2 Status of development of the IMP

NONS has been registered as a Class 1 medical device with a CE mark in the European Union in accordance with Regulation (EU) 2017/745 on medical devices. The Global Medical Device Nomenclature Code indication is: “nasal mucosa fluid dressing, antimicrobial”. In ECRAID-Prime NONS will be considered an IMP. It should be mentioned however that NO, nor other elements of the formulation are absorbed systemically after intranasal application.

NO is a molecule that is already approved by the FDA, Health Canada and the EU as a drug treatment for newborn babies that have pulmonary hypertension [16, 17]. For over two decades, inhaled NO has been delivered to the lungs as a drug in a vulnerable population without any reported safety sequalae [18]. Human clinical use and safety information for NO gas is substantial, and the dosage of NONS used in ECRAID-Prime is significantly lower than that has been approved by the regulatory drug agencies [1, 2, 17, 19].

NO does not occur and cannot be formulated differently other than by combining one nitrogen atom and one oxygen atom and is in a gas phase at room temperature. Consequently, there is no difference between endogenously produced NO in biological systems, pharmaceutical production, naturally occurring NO in the environment and the NO in NONS. NONS is a new formulation of the FDA-approved NO gas.

5.1.3 Description and justification of dosage and route of administration

NO will be administered **intranasally** (not inhaled into the lungs) six times per day [2 sprays each nostril, equivalent to 0.5 mL volume total per dose (4 sprays)], for seven days. NONS need to be administered upon awakening (dose 1), with five further doses (doses 2 to 5) administered approximately every 2-3 hours (minimum 1.5 hours apart) while awake. The last dose (dose 6) need to be administered at bedtime. The dosage and treatment duration is similar as in earlier published research showing that this NONS treatment regime accelerated clearance of SARS-CoV-2 from the nasal cavity [1].

Administration advice: Gently insert the bottle tip just into one nostril. Press on the other side of your nose with one finger to close off the other nostril. Aim slightly away from the center of your nose, point at the direction of the ear, and pump one spray. Sniff gently through the nose

while applying, do not inhale deeply. Exhale through your mouth. Ensure that the spray is held vertically while spraying.

The dosage of NO in ECRAID-Prime is substantially lower than that approved by the regulatory drug agencies for NO gas inhalation into the lungs.

5.2 Additional considerations for trials involving a medical device

Not applicable.

5.3 Preparation and labelling of the Investigational Medicinal Products

Participants randomised to NONS will be allocated an individual IMP pack according to the randomisation number, including one dual-chambered bottle of 25mL solution (12.5mL in each chamber of bottle), containing sufficient IMP for seven days of administration.

NONS will be labelled that the double-blind design of the study is effectively maintained throughout the study.

Example of an English label:

{Backbone text (if applicable)}

FOR CLINICAL TRIAL USE ONLY
Protocol: ECRAID-Prime EU Clinical Trial Registration no.: 2022-501707-27
Investigator: _____

Kit number: XXXXXX
Lot/Batch Number: BBBB-BB

Participant number: PRIME-I__I__I I__I__I I__I__I__I__I

Date dispensed: I__I__I I__I__I I__I__I__I__I
day month year

Content: 1 bottle of 25mL Nitric Oxide 5.35ppm*min over 30 minutes with 4 sprays (1 dose) nasal spray (NONS), or 25mL 0.9% saline solution nasal spray, ~45 doses per bottle for intranasal use

Instructions for use: 7 days, 6 times per day (2 sprays per nostril), see instructions for use of medical product

Storage Conditions: between 15-25°C Not to be used after: MM/YYYY

Sponsor: UMC Utrecht, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands
Telephone: +31 88 755 5555

KEEP OUT OF REACH OF CHILDREN Return packaging and unused medication

6 OTHER TREATMENTS AND RESTRICTIONS

6.1 Concomitant therapy

6.1.1 Permitted medication

Participants should continue to take their usual prescribed medications throughout the study period, and can take symptomatic respiratory infection treatments e.g. antipyretics, simple analgesia and antitussives. These treatments will be permitted before and during the study. Usual care medications will be recorded for the duration of the study (e.g. antibiotic, antiviral and pain/fever medication).

Participants requiring initiation of new medications or treatment for their respiratory infection during the seven days of IMP administration will be advised to contact the appropriate study staff personnel.

6.1.2 Prohibited medication

The following medications are prohibited for 7 days following randomisation and within 7 days before screening:

- NO donors/derivatives: isosorbide dinitrate, isosorbide mononitrate, nitroglycerine/glyceryl trinitrate, nitroprusside, nicorandil.
- Phosphodiesterase inhibitors: avanafil, sildenafil, tadalafil, vardenafil.
- Guanylate cyclase activators: riociguat, linaclotide.

Use of prohibited medications during the study will be documented as a protocol deviation. The decision about use of data from such participants is detailed in the statistical analysis plan.

6.1.3 Escape medication

As per master protocol.

6.2 Lifestyle restrictions

6.2.1 Contraception measures

Pregnant and breastfeeding women are excluded from this arm. See inclusion criteria and definitions in master protocol.

6.2.2 Other requirements

There are no other requirements.

7 TRACEABILITY, STORAGE, ACCOUNTABILITY AND COMPLIANCE

NONS should be stored between 15-25°C and should not freeze. NONS should be discarded on the expiration date printed on the bottle, or 60 days after first opening, whichever comes first.

8 METHODS

8.1 Study parameters/ endpoints

No blood samples will be collected.

8.2 Randomisation, blinding and treatment allocation
As per master protocol.

8.3 Study procedures
As per master protocol.
In addition, pregnancy should be ruled out by a negative urine pregnancy test for all women of child-bearing potential prior to randomisation.

8.4 Withdrawal of individual participant
As per master protocol.

8.5 Replacement of individual participants after withdrawal
As per master protocol.

8.6 Discontinuation of treatment of individual participants
As per master protocol.
In addition, a participant should discontinue treatment if:
- They experience headache, nose bleed, or burning sensation immediately after use of IMP. A physician should be consulted by the participant if symptoms persist.
- They become pregnant during IMP administration.

8.7 Premature termination of the study or arm
As per master protocol.

9 SAFETY REPORTING
9.1 Adverse events (AEs)
As per master protocol.

9.2 Serious adverse events (SAEs)
As per master protocol.

10 STATISTICAL ANALYSIS
For the primary analysis, NO nasal spray will be compared to saline nasal spray (see Appendix IIC: Saline). Superiority will be claimed if the posterior probability of superiority is greater than or equal to 0.988.

As a secondary analysis NONS will be compared to Usual Care (see Appendix IIA: Usual Care).

Interim analyses
The first interim analysis will occur when 150 participants have been recruited to NONS (and 150 to Saline) and have had the opportunity to be followed for 28 days from randomisation. A second interim analysis will occur when 225 participants have been recruited to both arms. Recruitment to NONS will stop early for futility at either interim analysis if the posterior

probability of superiority is less than 0.5, and for superiority if this probability is greater than 0.999.

11 ETHICAL CONSIDERATIONS

As per master protocol.

12 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

As per master protocol.

13 STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

In vitro, NO has an immediate virucidal action against all VOCs of SARS-CoV-2 and other respiratory pathogens [3]. NO alters the structural integrity of viral proteins through nitrosylation and palmitoylation reduction; interferes with the fusion of S protein to its cognate host receptor ACE-2; and impedes viral protease activity resulting in the inhibition of viral RNA replication [4-7]. The inherent low pH (3.5) and virion trapping capacity (HPMC) of NONS augments the antiviral activity of NO.

b. Previous exposure of human beings

Efficacy and Safety Data – Previous treatment RCTs

1. UK COVID-19 Phase 2b – Q1 2021 [2]

Methods: 6 doses per day for 8 days of treatment with NONS compared to placebo in participants mild COVID-19 (n=80). Primary objective was difference in SARS-CoV-2 log10 viral reduction from Day 1 to Day 6.

Efficacy: SARS-CoV-2 viral load reduction was observed within 24 hours, and a 99% reduction within 72 hours, with NONS treatment. The difference in viral load between NONS and placebo was statistically significant for all three days ($p<0.05$ at Day 2, 4 and 6 for NONS compared to placebo).

Safety: No unexpected AEs occurred during the study. No subject withdrew from the study due to an AE. There were no complications, misuse, or overdoses through self-administration of NONS.

2. India COVID-19 Phase 3 – Q4 2021-Q1 2022 [1]

Methods: 6 doses per day for 7 days of treatment with NONS compared to an active placebo (containing preservative (benzalkonium chloride 0.01%) in normal saline) in subjects with documented mild COVID-19 18 to 70 years of age (n=306). Primary objective was difference in SARS-CoV-2 log10 viral reduction from Day 1 to Day 8

Efficacy: In non-hospitalized adult Asian patients with mild symptomatic COVID-19, self-administered NONS had a statistically significant greater mean reduction in SARS-CoV-2 RNA log10 copies/mL over seven days of treatment compared to placebo. NONS subjects were 35.4% more likely to achieve RT-PCR negative status 4 days sooner than the placebo group (Day 8). Clinically, more subjects receiving NONS were asymptomatic with no detectable

SARS-CoV-2 RNA near the end of the study compared to placebo (Day 16 treatment difference 12.6%, 95%CI: 0.1-25.1, p=0.038).

Safety: Overall, 6.5% of the NONS group had mild AEs, primarily nasal discomfort (3.3%) compared to 2.7% in Placebo (1.3% nasal discomfort). No unexpected AEs occurred during the study. No subject withdrew from the study due to an AE. No SAEs occurred. No clinically significant, nor other changes were observed while on NONS in vital signs, EEGs, systemic blood oxygenation, methemoglobin levels, clinical laboratories, or physical examinations.

3. Bahrain COVID-19 Phase 3 – Q4 2021-Q1 2022 [19] (not published, per IB)

Method: 6 doses per day for 7 days of treatment with NONS compared to placebo (active) in participants with documented mild COVID-19 or asymptomatic high-risk participants with COVID-19 (n=501). Primary objective was to determine the difference in access of urgent healthcare services.

Efficacy: No significant difference in the primary endpoint between NONS and placebo group.

Safety: No SAEs were reported. No subject in the trial reported nasal discomfort; <1% of the participants experienced any AE. One subject in the NONS treatment group experienced one mild AE of finger skin peeling. Three subjects on placebo experienced AEs. Other safety data pending.

Efficacy and Safety Data – Previous and/or ongoing prevention RCTs

1. Thailand post-exposure prophylaxis prevention observational trial Q1 2022 [19] (not published, per IB)

Method: 4 to 6 doses maximum per day for 10 days of NONS compared to a non-NONS control group in participants at high-risk of becoming infected with SARS-CoV-2 after close contact with a COVID-19 patient. Participants were 18 to 24-year-old university students who had shared a living space with a documented recently infected COVID-19 patient; 203 participants received NONS and 422 participants received standard of care during quarantine (N=625). Primary objective was infection prevention (measured by SARS-CoV-2 testing).

Efficacy: Infection rate comparison (N=625) revealed 6.4% (13/203) of participants that received NONS developed a SARS-CoV-2 infection whereas 25.6% (108/422) non-NONS control group participants became infected (p<0.0001).

Safety: No SAEs were reported. 34.5% (70/203) of participants receiving NONS answered the safety questionnaire. 11.4% experienced an AE of mild nasal burning/irritation with NONS.

2. Global COVID-19 Phase 3 prevention RCT Q1-3, 2022 [19]

Method: 3 doses per day for 28 days. Enrollment in Sri Lanka (+3,000 planned) and Canada (+1,500 planned). Primary objective is NONS difference in preventing infection (symptoms and SARS-CoV-2 virus detection) vs placebo.

Enrollment in Sri Lanka started 13 January 2022, Canada started enrolling 13 May 2022.
Safety (1st DSMB safety review conducted 5 May 2022); safety monitored daily. SAE: 1 hospitalization (COVID-19). AE: 562 AEs have been reported (blinded; combined NONS and placebo), most likely infection-related. 90% of AEs were mild in severity, with 9% considered

moderately severe. 95% of the AEs were considered unrelated to therapy, with 2% possibly, and 3% probably related to therapy. The top 6 AEs reported have been stuffy/running nose (166), headache (85), cough (59), muscle/body ache (47), sore throat (44) and low energy/tiredness (41).

As of 30 November 2022 (Part A), 1264 participants were enrolled in Sri Lanka; ET: 13; COVID-19 positive cases: 16; AEs: 704. 125 participants were enrolled in Canada; ET: 11; COVID-19 positive cases: 7; AEs: 22. The total number of AEs (blinded data) is 726, with 659 mild severity (90.8%), 63 moderate severity (8.7%), 4 severe (0.5%); 11.8% was considered related. Nasal irritation was reported by 30 (4.1%); nasal burning by 25 (3.4%), nosebleed by 1 (0.1%) and headache by 116 (16.0%). Segregation into those caused by NONS or Placebo will not be known until the trial is completed.
Part B will commence in 2023 reflecting the changing landscape of the SARS-CoV-2 pandemic, coemergence of Influenza with COVID-19, assessing infections in both symptomatic/asymptomatic participants and utilizing the current dosing regimen (used globally as a medical device).

c. Induction of the mechanism in animals and/or ex-vivo
There is *in vitro* work supportive of the hypothesis that NO has direct anti-SARS-CoV-2 activity, although this is very limited. No *in vivo* evidence is available in animal models. A much larger body of preclinical data is supportive of an overall antiviral effect, including against SARS-CoV-1 [4] and other respiratory viruses [3, 19]. Most pre-clinical literature is supportive of an anti-inflammatory role for NO, although the mechanisms involved are varied and non-specific. There is some evidence of increased levels of NO in chronic inflammation. Animal data is suggestive of NO playing a role in nasal barrier function [19].

Antiviral effects of NO have been described in experimental models of influenza. Three strains of influenza (A and B) were exposed to gaseous NO for 180 min before and after infection of MDCK cells. Pre-infection exposure resulted in complete inhibition of infectivity in all three strains. Post-infection exposure reduced infectivity by approximately 30% [7]. However, in tissue models of rhinovirus infection using lung fibroblast and epithelial cell lines, pre-treatment with NO donors had no effect on viral replication or IL-8 production [20].

d. Selectivity of the mechanism
NO generated in NONS remains confined to the nasal cavity, without systemic absorption [1, 2, 19].

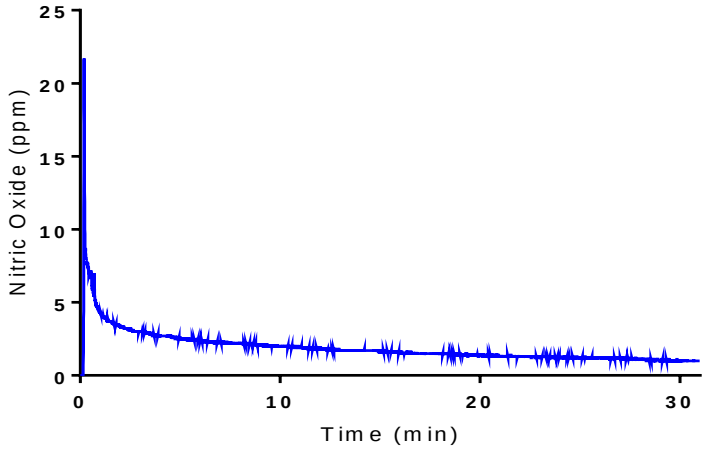
Systemic absorption of NO is known to produce vasodilation (lowering of systolic and diastolic blood pressures) and hypoxemia due to methemoglobinemia-induced transient O_2 desaturation. These events are considered clinical safety concerns and issues with NO gas inhalation in the lungs and not with intranasal administration.

The onset, peak (magnitude), and duration of extravascular NO ppm concentrations generated and released post NONS dose (5 mL) is illustrated in **Figure 1**. Based on the NO ppm concentration observed immediately after administering a standard NONS dose (total of 4 sprays, 2 per nostril; 0.5 mL equivalent), the onset of NO generation is instantaneous with a peak maximal NO concentration of 1.89ppm in under <1 second. The concentration of NO rapidly declines to 0.47 ppm at 30 seconds, 0.23ppm at 5 minutes, 0.18ppm at 10 minutes,

0.13ppm at 20 minutes and 0.11ppm at 30 minutes post 0.5 mL NONS dose equivalent, or 0.18ppm (average/minute released) with 4 sprays (1 dose).

The mean total NO expected nasal exposure is 5.35ppm*min (AUC) from a NONS dose (i.e., 4 spray/dose per 0.5mL) over 30 minutes ($AUC_{0\text{-}30min}$). Thirty percent of this concentration exposure occurs over the first 5 minutes (NO 1.65ppm*min generation, $AUC_{0\text{-}5min}$). The virucidal activity of NONS is typically established within 5 minutes of NO generation from NONS in antiviral laboratory assessments performed to date (NONS IB). NO concentrations are not captured or recorded after 30 minutes of the mixing of the solutions.

Figure 1. Non-systematic NO release pharmacokinetics (0.5 mL NONS Dose)



Lack of systemic NO absorption from exogenously generated gas.
The NO generated and released from NONS is in a gaseous-liquid state. NO released locally within the nasal cavity is extravascular to the nasal (host) microvilli-equipped epithelial cells (ciliated and non-ciliated). Gases are typically not systemically absorbed without an alveoli/capillary unit as is only found in the pulmonary system. NO transferred to the lungs from nasal administration is not expected due to the observation that the smallest particle sizes of NONS released from the spray bottle are of a magnitude ten times larger than the size required for systemic absorption through the alveoli/capillary unit [19].

NO dose proportionality released from NONS vs inhalation NO
The relatively low dose of NO produced from NONS is in the order of 0.5% (0.11ppm (at 30 minutes; or 5.35ppm*min over 30 minutes released with 4 sprays [1 dose]) vs 20ppm) of used with gas inhalation dosing. In addition, the dose of NO gas used via inhalation is administered continuously for hours/days, while the gas released from a dose of NONS is non-continuous, finite, and short-lived [19].

The lack of systemically absorbed NO gas generated and released from the NONS formulation is expected to establish a safety profile that has a very high benefit to risk ratio when administered in clinical practice [1, 2]. Essentially no systemic drug-drug interactions are anticipated [19].

e. Analysis of potential effect
NONS may cause adverse drug reactions. The following are considered mild in severity:
- Nasal burning or irritation

- Headache
- Skin rash (facial & hands, if sprayed directly on face or hand)
- Nosebleeds

Participants should contact the study team, or their GP if nasal burning persists more than 10 minutes, or any of the adverse drug reactions are severe or persistent.

The administration of NO nasal spray is considered a local therapy delivered and confined to the nasal cavity, lacking systemic absorption of NO. When NO is administered as a gas, for inhalation into the lungs, the following possible rare but potentially severe adverse drug reactions have been reported:

- Facial flushing
- Rapid heartbeat
- Migraine-like headache
- Dizziness
- Nausea
- Blurred vision
- Rapid breathing, shortness of breath
- Fainting/severe weakness

It is not expected that these potentially servere adverse drug reactions occur from intranasal NONS application. However, the responsible clinician or the trial team should be contacted if the participant experiences unexpected complaints, like severe migraine-like headache, rapid heartbeat, dizziness, fainting, blurred vision or severe facial discomfort. Any participant experiencing symptoms of methemoglobinemia (i.e., cyanosis or changes in skin color with or without low oxygen saturation on pulse oximetry), should have therapy terminated and appropriate clinical management.

f. Pharmacokinetic considerations

NO generated from NONS is not systemically absorbed. The plasma half-life (from lung inhalation) has been reported to be less than 1.5 seconds.

g. Predictability of effect

SARS-CoV-2 RNA concentration reduction (copies/mL) has been documented [1, 2].

h. Interaction with other products

No drug-drug interactions are expected since NO lacks systemic absorption from the nasal cavity [19].

i. Managing of effects

After being on the market as a medical device in multiple countries (>1.5 years; with 350,000 bottles dispensed without any post-market safety issues [another 950,000 have been ordered and shipped)]), and from its administration in multiple treatment and prevention trials (including an ongoing global prevention trial), there have been no SAEs, no hospitalizations, nor deaths due to NONS.

j. Study population

NONS therapy is intended for non-hospitalized patients with COVID-19 and COVID-like-illness, who are otherwise stable. Pregnant/breastfeeding women and women of childbearing potential not adequately protected against pregnancy will be excluded.

13.2 Overall synthesis of the direct risks for the research subjects

The clinical experience to date, from pharmacovigilance safety monitoring (>1 year) and RCTs, suggest a positive benefit/risk ratio of NONS. Due to its relatively low dose, intermittent dosing, confinement to the nasal cavity and lack of systemic absorption risks are negligible. For this section reference is also made to the latest Investigators Brochure.

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