ADDENDUM 2 TO PROTOCOL LDOS-21-001

Protocol Title: A virtual Phase 2 randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of the combination of famotidine and celecoxib as a post-exposure prophylaxis (PEP) for newly-infected COVID-19 patients

Protocol Number: LDOS-21-001-02

Study Phase: 2

Short Title: LEAP-CT for evaluation of post-exposure prophylaxis for newly-infected COVID-19 patients

Sponsor Name: Leidos, Inc.

Legal Registered Address:

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Regulatory Agency Identifier Number(s): IND 153669

Approval Date: xx April 2022

Date: 11 April 2022

Version: 2.0

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Leidos, Inc.

Responsible Medical Officer:

[redacted]

Date

Sponsor's Authorized Officer:

[redacted]

Date

Medical Monitor Name and Contact Information:

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the **Leidos LDOS-21-001 and LDOS-21-001-01** study protocols and agree to conduct the studyin accordance with these protocols, all applicable government regulations and the principles of the ICH E6 Guidelines for Good Clinical Practice. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator	**Signature of Investigator**
Date	

PROCEDURES IN CASE OF EMERGENCY

In case of emergency, Table 1 provides contact information as reference.

Table 1: Emergency Contact Information

Role in Study	Name	Address/ Telephone Number
Clinical Study Leader		
Responsible Physician		
Drug Safety Physician		
24-Hour emergency contact		

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
V1.0 Initial Version	12 August 2021
V1.1, Amendment 1	07 December 2021
V2.0, Amendment 2	07 March 2022

Amendment 2

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
3. Study Population	Added language on recruitment process and compensation of participants	Recruitment numbers have been low and most potential leads have inquired about monetary compensation. Included recruitment process to clarify question
1.1 and 3.2 Inclusion Criteria, 2	Added FDA-authorized at-home antigen positive test results to inclusion criterion, with need for confirmatory PCR testing while participant goes through screening	Recruitment numbers have been low and potential leads have been using the U.S. Government-provided at-home antigen tests instead of seeking a PCR test.
Table 5 Schedule of Activities	Added row for collecting a nasal swab for confirmatory PCR testing. Deleted Day -7 to Day -1 from header row.	FDA requested any prescreened participant that was positive by at-home antigen testing be confirmed positive by PCR. Deleted the timeframe as it was causing confusion with site personnel.
5.1 Screening	Added language to the phlebotomy visit regarding collecting a nasal swab for confirmatory PCR testing for those positive by at-home antigen test at prescreening	The FDA requires a confirmatory PCR positive test result for those participants that were consented using a positive test result from an at-home antigen test.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Please refer to the Master Protocol LDOS-21-001 for a comprehensive background and rationale for this study of a combination of famotidine and celecoxib as a post-exposure prophylaxis (PEP) for newly-infected COVID-19 patients.

This study (**LDOS-21-001-02**) is designed to test the efficacy and safety of combinations of two well-understood agents—famotidine and celecoxib. Each of these agents separately demonstrate clinical activity in mitigating COVID-19 disease symptoms or severity, and each of which appear to have separate and complementary mechanisms of action.

Study Description: This is a virtual Phase 2 randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of the combination of famotidine and celecoxib as a post-exposure prophylaxis (PEP) for newly-infected COVID-19 patients. Qualifying patients will have been confirmed positive for COVID-19 and have symptoms of WHO Ordinal Scale for Clinical Improvement with scores of ≤3 on the 11–point scale (Table 2), and will be randomly assigned, in a 1: ratio, to one of two regimens, with 659 participants per group, as follows:

- **Group 1 (Study Product)**: 80 mg famotidine (PO) QID + celecoxib 400 mg first dose, followed by 200 mg (PO) BID for 5 days. Following this 5-day period, participants will continue their 80 mg famotidine QID treatment for an additional nine days.

  Group 2 (Reference Comparator): Matching placebo for famotidine and celecoxib respectively, QID + BID for five days. Following this 5-day period, participants will continue to receive matching famotidine placebo, QID, for an additional 9 days.

There will be a subsequent follow-up period of 90 days from Baseline (Day 1 of treatment).

Table 2: WHO 11–point Clinical Progression Scale

Score	Descriptor	Patient State
0	Uninfected; no viral RNA detected	Uninfected
1	Asymptomatic; viral RNA detected	Ambulatory Mild
2	Symptomatic; independent	Ambulatory Mild
3	Symptomatic; assistance needed	Ambulatory Mild
4	Hospitalized; no oxygen therapy	Hospitalized Moderate
5	Hospitalized; oxygen by mask or nasal prongs	Hospitalized Moderate
6	Hospitalized; oxygen by NIV or high flow	Hospitalized Severe
7	Intubation and mechanical ventilation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200	Hospitalized Severe
8	Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or vasopressors	Hospitalized Severe
9	Mechanical ventilation, pO2/FiO2 <150 and vasopressors, dialysis, or ECMO	Hospitalized Severe

Score	Descriptor	Patient State
10	Dead	Dead

Study Objectives and Endpoints: The objectives of the study are to evaluate the safety and efficacy of famotidine and celecoxib when used as a treatment for COVID-19. The study specific objectives and endpoints are described Table 3 and within Section 1.4.

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
Efficacy	The percentage of patients with at least one COVID-19–related medically attended contact, due to increased symptom severity, through Day 30 in both the placebo and the overall trial population, or incidence of death (all-cause mortality). Medically attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, hospitalization.
Secondary	
Safety	Incidence of Related Serious Adverse Events (SAE) Incidence of discontinuation due to related SAE Oxygenation Status (oxygen saturation ≤ 94%, necessitating supplemental oxygen, as measured by daily pulse oximeter ratings)
Efficacy	The percentage of participants with at least three COVID-19–related medically attended contacts due to increased symptom severity, through Day 30.
Exploratory	
Efficacy	Rate of hospitalization, as well as all-cause mortality rate. Additionally, multiple Patient-Reported Outcome (PRO) endpoints will be used to establish how participants feel and function in relation to disease and treatment. These endpoints will include daily ratings of symptom type and severity. Symptoms will be captured using a 0-10, 11-point numerical rating scale ranging from “None” to “Extreme.” Daily ratings of perceived incapacity will also be obtained using a 0-10, 11-point numerical rating scale ranging from “No Limitation” to “Extreme Limitation." At the conclusion of their participation, participants will also report on their global impression of therapeutic change using an established 7-pt Patient’s Global Impression of Change Scale (PGIC), their belief regarding active vs. placebo group assignment, and their qualitative impressions of their illness experience elicited through narrative probes. In addition to the above subjective measures, daily body temperature ratings will be captured and recorded.

Inclusion criteria:

1. Participant must be at least 18 years of age, inclusive, at the time of signing the Informed Consent.
2. Confirmed SARS-CoV-2 PCR positive or positive by FDA-authorized at-home antigen test within 5 days of enrollment (i.e., signing the ICF), as shown by medical history and reported PCR or antigen test result; confirmatory PCR testing is required for participants with an antigen-positive test result before starting study medication.
3. Reports having one or more symptoms consistent with SARS-CoV-2 (as defined in Appendix 3, Table 4 of the Master Protocol, LDOS-21-001).
4. COVID-19 Diagnosis must be WHO Grade <3, as referenced in Section 1.1, Table 2
5. Contraceptive use by men or women should be consistent with **Appendix 4** of the Master Protocol (**LDOS-21-001**).
6. Reliable access to the Internet via a browser installed on personal device or computer.
7. Capable of understanding and providing of signed informed consent.

Exclusion criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Pregnancy or breastfeeding
2. Ongoing antiviral or antiretroviral treatment
3. Known history of HIV
4. Ongoing anti-inflammatory treatment that cannot be temporarily discontinued during the study. This includes nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids – including Dexamethasone (dexamethasone administration restricted to recommended standard of care use per NIH COVID-19 Guidelines)
    a. drugs dependent on gastric pH for absorption, e.g., dasatinib, delavirdine, mesylate, cefditoren, and fosamprenavir
    b. tizanidine (CYP1A2) substrate,
    c. drugs that interfere with hemostasis (e.g., warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]),
    d. angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta-blockers,
    e. diuretics,
    f. digoxin.
5. Ongoing treatment that cannot be temporarily discontinued during the study, with: antimalarials, antiarrhythmics, tricyclic antidepressants, natalizumab, quinolones, macrolides, agalsidase alfa and beta
6. Ongoing famotidine, celecoxib or other COVID-19 clinical investigational treatment(s) within the past 30 days, or current participation in another investigational clinical trial.

7. History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
8. History of immunosuppression
9. Rejection of participation by Principal Investigator or Sponsor
10. Any contraindication for famotidine or celecoxib treatment:
    a. Famotidine or celecoxib hypersensitivity
    b. Retinopathy, visual field or visual acuity disturbances
    c. History of cardiovascular disease, such as congestive heart failure, QT prolongation, myocardial infarct, bradycardia (< 50 bpm), ventricular tachycardia, other arrhythmias
    d. Myasthenia gravis
    e. Psoriasis or porphyria
    f. History of renal failure/dialysis or a glomerular clearance <60 mL/min
    g. History of severe hypoglycemia
    h. Moderate or severe hepatic impairment, e.g., Child-Pugh Class B or C
    i. Known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history or experience with other CYP2C9 substrates, such as warfarin and phenytoin.

Data Collection: Throughout the study, participants will enter data using their personal web-enabled devices via a secure internet URL, into an adaptive self-reporting platform ([redacted], and transmitted to the ClinTrial database. This will allow for tracking increases and decreases in symptom severity and capability to perform tasks throughout the treatment phase of the study and, subsequently, through the follow-up phase. Participants will be able to report their symptoms, potential adverse events (AEs), and all other required data, once daily each day. Tracking symptoms during follow-up will help establish and identify the emergence of new symptoms or return of previously noted symptoms following treatment.

Data Safety Monitoring Board: An independent Data Safety Monitoring Board (DSMB) will be established to monitor safety data at regular intervals to ensure the continuing safety of participants enrolled in the study. Summary data tables and listings, as well as any individual participant data will be provided to the DSMB by unblinded personnel (e.g., independent unblinded biostatistician), who will not be the same staff responsible for the analysis and operational aspects of the study. Summary data may be initially provided in semi-unblinded fashion (e.g., participants sorted by study treatment regimen, without disclosure of the actual treatment administered). Should the DSMB require fully-unblinded data, these tables and listings will then be provided.

Statistical Methods: The study will aim to enroll up to 1465 participants, which assumes a 10% screen failure rate, with a final allocation of 659 participants in the treatment arm and 659 in the control arm.

This sample size of ensures a power of 90% at a 2-sided α of 5%, assuming a 1:1 randomization, a placebo rate of 6% (of participants with at least one COVID-19–related medically attended contact, due to increased symptom severity, or incidence of death due to COVID-19 through Day 30) and an assumed relative risk reduction of 65% to 2.4% in the active treatment arms. The statistical test of the null hypothesis of no between-group difference in proportions, as specified

in the primary endpoint, will be tested using a χ^2 test at a two-sided 5% significance level. An interim analysis for futility will be performed after 50% of participants have completed the primary endpoint assessment at day 30. Safety analyses will be performed on the Safety Population, consisting of all participants who are randomized and received study drug, analyzed by actual treatment arm. A more detailed description of the statistical methods can be found in Section 7.

Protocol Title: A virtual Phase 2 randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of the combination of famotidine and celecoxib as a post-exposure prophylaxis (PEP) for newly-infected COVID-19 patients.

Short Title: LEAP-CT as a post-exposure prophylaxis for newly-infected COVID-19 patients.

Rationale: Please refer to the Master Protocol LDOS-21-001 for a comprehensive background and rationale for this study of a combination of famotidine and celecoxib as post-exposure prophylaxis (PEP) for newly-infected COVID-19 patients.

Overall Design: This is a Phase 2, randomized double-blind placebo-controlled decentralized virtual study in which outpatient participants, newly diagnosed for COVID-19, will be randomized in a 1:1 ratio to one of two study groups (1 treatment group and 1 control group). The study is designed as a virtual trial in that it will be conducted, *in situ,* with home-based participants entering self-assessments via a web-enabled adaptive platform – [redacted] The participants will be under the oversight of regionally based investigators who will be responsible for study conduct and the review of blinded data on a periodic basis.

Intervention Groups and Duration: The treatment regimen for this study is shown in Table 4.

Table 4: Study Interventions

Regimen	Dose	# of Participants
Group 1	80 mg famotidine (PO) QID + celecoxib 400 mg first dose, followed by 200 mg (PO) BID for 5 days. Following this 5-day period, participants will continue their 80 mg famotidine QID treatment for an additional nine days.	659
Group 2	Matching Placebo for famotidine and celecoxib respectively – QID + BID for five days. Following this 5-day period, participants will continue to receive matching famotidine Placebo, QID, for an additional 9 days.	659

Disclosure Statement: This is a Phase 2 randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of the combination of famotidine and celecoxib as a post-exposure prophylaxis (PEP) for newly-infected for COVID-19 patients. These participants will not be hospitalized at enrollment, and all study activities will be performed at the participant's home. Investigational product and matching Placebo will be shipped directly to the participant from the Sponsor's supplier. There will be no other physical location where participants are seen. Virtual research teams will be organized by U.S. geographical region under the oversight of a Principal Investigator licensed to practice in the state(s) in which participants reside. Each site or group of affiliated sites will be required to designate at least one physical location to serve as a research facility for storage of any paper documents generated, mail correspondence or location

for inspection activity. This designated location will be listed as a research facility under Section #3 of Form FDA 1572.

Number of Participants: Approximately 1800 participants will be screened to achieve 1465 randomly assigned to study intervention and at least 1318 evaluable participants for an estimated total of 659 evaluable participants per group.

Study Design: The study design is shown schematically in Figure 1.

Schedule of Assessments: The participants will have responsibility for entering self-assessment of symptom severity, body temperature, blood oxygen concentration (spO2) using Sponsor-supplied devices, using the web-based [redacted] platform. The study Schedule of Assessments is shown in Table 5.

Figure 1: Study Design

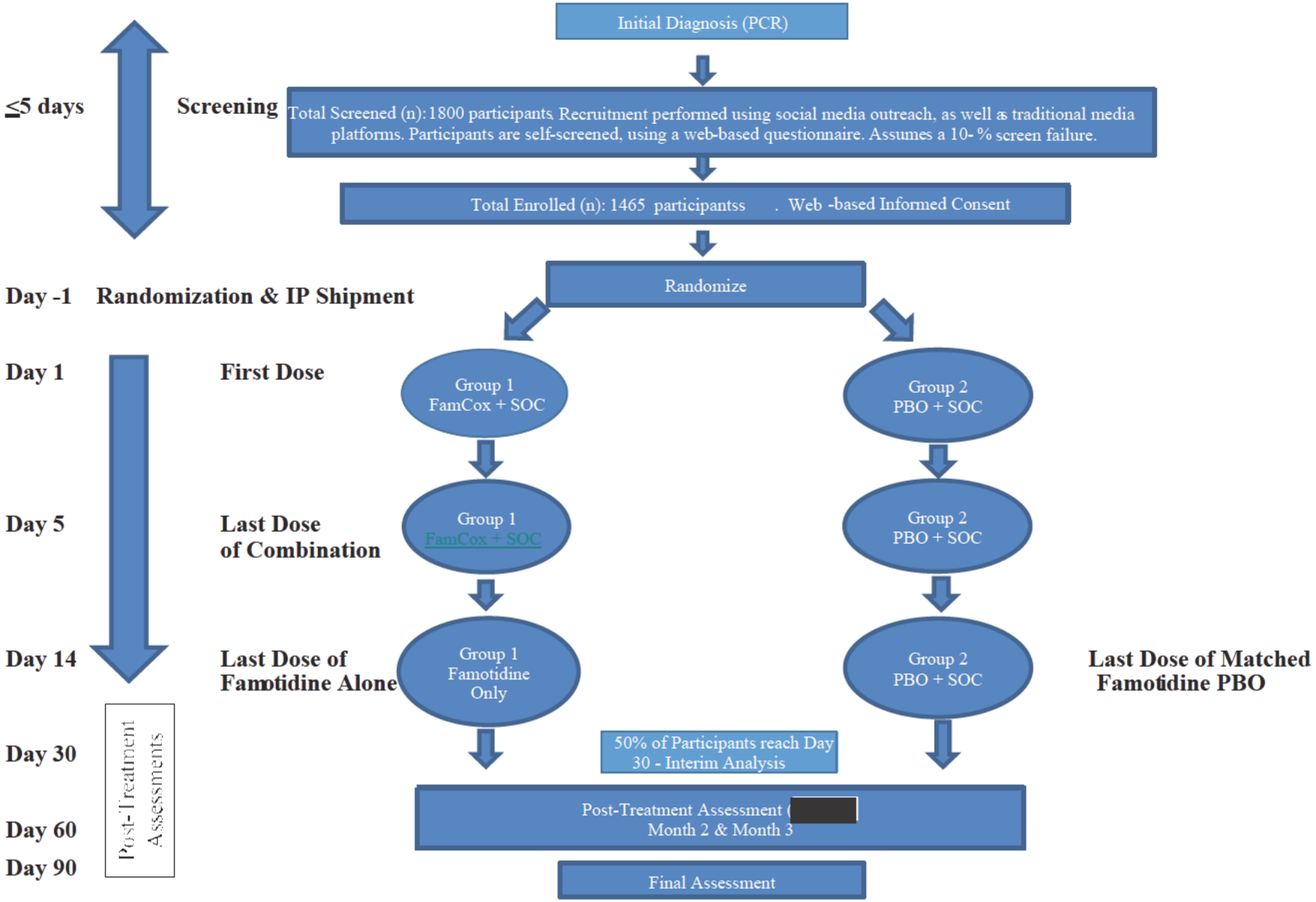

Table 5: Schedule of Assessments

Study Activities and Assessments	**Screening & Randomization** [1]		**Treatment Period**			**Observation Period** [2]	
Visit Number [3]	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day		**Day 1 Baseline/ Start of Treatment**[4]	**Day 7(±1)**	**Day 14 (±1)**	**Day 30(±1) End of Treatment**	**Day 60**	**Day 90**
Informed consent[5]	X						
Inclusion and Exclusion criteria	X	X					
Demographics	X						
Medical History, including weight reporting[6]	X						
Concomitant medication review	X	X	X	X	X		
Blood draw for comprehensive metabolic panel (mobile phlebotomy & laboratory service)	X		X	X			
Nasal swab for confirmatory PCR test for at-home antigen positive test prescreened participants (mobile phlebotomy & laboratory service)	X						
Randomization and initiation of drug shipment[7]	X						
Review of reported baseline symptoms		X		X			
Confirmation of Study Drug Receipt & Initial Dose		X					
Confirmation of Study Drug Return Shipment[8]					X		
Review of eDiary for study drug compliance[9]			X	X	X		
Adverse Events Review		X	X	X	X		
Participant Intake of study drug		Daily on Days 1–14					

Study Activities and Assessments	**Screening & Randomization** [1]		**Treatment Period**			**Observation Period** [2]	
Visit Number [3]	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day		**Day 1 Baseline/ Start of Treatment**[4]	**Day 7(±1)**	**Day 14 (±1)**	**Day 30(±1) End of Treatment**	**Day 60**	**Day 90**
Symptom questionnaires, spO2, and temperature		Daily for the entire treatment and observation period (Days 1–90)					
Mobile ECG		X	X	X			

[1] Participant will complete demography, medical history, concomitant medications, and questions regarding inclusion and exclusion criteria [including results of SARS-CoV-2 PCR test and self-administered urine pregnancy test] via [redacted] Site will review participant responses and confirm information with participant by Visit 2.

[2] During the observational period, while participant is not taking any IP, participant will record long term symptoms for Covid-19, but will be directed to consult with his/her primary care physician (PCP) for follow up of any health changes. Planned contacts with participants on Days 60 and 90 will be performed by study support staff only to confirm continued participation in the study.

[3] All participant visit activities will be performed remotely.

[4] Visit 1/participant informed consent must be performed within 5 days of a positive PCR or at-home antigen test, as per inclusion criteria. As IP will be shipped to the participant upon randomization, treatment start date (Visit 2/Day 1) may not occur until a few days after initiation of IP shipment. Participant will start treatment after IP receipt and review of inclusion/exclusion criteria with site. Date of first IP intake will always be considered Day 1, even if IP shipment is delayed outside of expected timeframe. If IP intake is delayed due to shipment, this will not be considered a protocol deviation.

[5] Participant will complete Informed Consent Process via [redacted]

[6] Medical history should include relevant history from within the past 3 years, with inclusion of relevant medical events within the past 5 years.

[7] IP will be shipped directly from drug depot to participants after randomization occurs within [redacted] Site investigator will confirm participant eligibility Visit 2.

[8] Participant will be provided return envelope for return of IP directly from participant to drug depot. At Visit 4, site will confirm with participant that he/she has shipped the IP back to the depot. Depot will be responsible for performing IP accountability.

[9] Participant eDiary review will be performed by the clinical site staff.

1.2. Background

Refer to the Master Protocol (**LDOS-21-001**) for a comprehensive background discussion. For this study, a secure, adaptive, interactive source data collection platform, [redacted] will be used. Because the platform is web-enabled, it provides a means for real-time data collection by the participant or study staff through any device that can access the internet.

1.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of each of the investigational products may be found in the Package Insert for famotidine and celecoxib respectively, and are provided in the Investigator's Brochure.

Refer to the Master Protocol (**LDOS-21-001**) for overall discussion of Benefit/Risk. The factors discussed here are specific to this study in home-based patients. Table 6 details the potential benefits, risks, and mitigations associated with study participation.

Table 6: Benefits, Risks, and Mitigations

Factors	Discussion	Evidence and uncertainties
Analysis of condition	COVID-19 Progression	Patients with COVID-19 disease can present with a range of mild-to-severe non-specific clinical signs and symptoms, which develop two-to-fourteen days after exposure to SARS-CoV-2. These symptoms include cough or shortness of breath, and at least two of the following: fever, chills, repeated rigor, myalgia, headache, oropharyngitis, anosmia, and ageusia. More severe symptoms warranting hospital admission include difficulty breathing, a persistent sense of chest pain or pressure, confusion or difficulty to arouse, as well as central cyanosis. Of hospitalized patients, 33% develop Acute Respiratory Distress Syndrome (ARDS), the most common cause for admission to the ICU; approximately 28% of patients admitted to the ICU will die
Current Treatment Options	Only one pharmacological agent (remdesivir) has been FDA-approved for the treatment of hospitalized COVID-19 patients.	Currently, there is no FDA-approved therapy for treating the early symptoms of COVID-19 and mitigating disease progression. Clinical management consists of supportive care, including ventilation in case of respiratory failure. Remdesivir and dexamethasone are not applicable treatment options for this outpatient study.
Benefit	Famotidine and Celecoxib have shown efficacy alone, and in (limited) combination, against viral mechanisms.	As noted in the Master Protocol, each of the two drugs in the combination therapy have been approved by FDA and are available either OTC or by prescription. Published reports indicate that each may independently act to reduce the morbidity and mortality associated with host responses to SARS-CoV-2 infection in those patients that develop COVID-19.

Factors	Discussion	Evidence and uncertainties
Risk	Study treatments (IP) in combination and at proposed dosages and regimens.	The two investigational products have a long history of use as both prescription and over-the-counter products. They have demonstrated acceptable safety profiles in their labelled indications and usage. There are limited data available, to-date, of the proposed investigational products in combination, and at the proposed dosages and regimens for the proposed indication. However, there are studies of famotidine (400 mg PO) and celecoxib (200 mg PO, BID) in combination against COVID-19 in 61 patients (Personal communication from [redacted] 15 March 2021). These have shown only small incidences of adverse events (one patient hospitalized and one incidence of allergic reaction in the former study).
Risk Management	Study Treatment	If intolerable side effects occur during the study, participants will be withdrawn from the trial in the participant's best interest. Patients with a history of allergic reactions or other significant uncontrolled medical conditions will be excluded from the study. In the event of adverse events or reactions, trained health professionals at the study site will take the appropriate measures for treatment, advice, or withdrawal from study.
	Study procedures	Patients will be carefully screened for any exclusion criteria to any of the planned study procedures, and will be excluded if the procedure is deemed to pose unacceptable safety risks to the patient.
	Safety Oversight	An independent DSMB will monitor the study progress for trends indicating unfavorable risk or safety profile.

1.4. Objectives and Endpoints

Study Description: This study (LDOS-21-001-02) is a virtual Phase 2 randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of the combination of famotidine and celecoxib as a PEP for newly-infected COVID-19 patients. This study is designed to test the efficacy and safety of combinations of two well-understood agents: famotidine and celecoxib. Each of these agents separately demonstrate clinical activity in mitigating COVID-19 disease symptoms or severity, and each of which appear to have separate and complementary mechanisms of action. Qualifying patients will have been confirmed COVID-19 – positive, and have symptoms of WHO Ordinal Scale levels ≤3, and will be randomly assigned, in a 1:1 ratio, to one of two regimens, with 659 participants per group, as follows:

- **Group 1 (Study Product)**: 80 mg famotidine (PO) QID + celecoxib 400 mg first dose, followed by 200 mg (PO) BID for 5 days. Following this 5-day period, participants will continue their 80 mg famotidine QID treatment for an additional nine days.

- **Group 2 (Reference Comparator)**: Matching Placebo for famotidine and celecoxib respectively, QID + BID for five days. Following this 5-day period, participants will continue to receive matching famotidine Placebo, QID, for an additional 9 days.

There will be a subsequent follow-up period of 90 days from Baseline.

1.4.1. Objectives

The objectives of the study are to evaluate the safety and efficacy of famotidine and celecoxib when used as a treatment for COVID-19.

1.4.2. Endpoints

Primary efficacy endpoint will include the percentage of participants with at least one COVID-19–related medically attended contact, due to increased symptom severity, through Day 30 in both the placebo and the investigational treatment population, or incidence of death (all-cause mortality). Medically-attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, hospitalization.

Secondary endpoints will include the incidence of related serious adverse events (SAEs) and the incidence of discontinuation due to related SAEs, as well as oxygenation status (oxygen saturation ≤ 94%, necessitating supplemental oxygen as measured by daily pulse oximeter ratings).

Exploratory endpoints will be evaluated for all study participants. The rate of hospitalization and all-cause mortality rate will be assessed for all participants. Additionally, multiple PRO endpoints will be used to establish how participants feel and function in relation to disease and treatment. These endpoints will include daily ratings of symptom type and severity from which estimates of symptom onset and duration can be derived, along with the tracking of dynamic trends over time. Symptoms will be captured using an 11–point numerical rating scale (NRS) ranging from “None” to “Extreme”, which corresponds to 0–10. The default symptom list provided to participants will include labels for 20 symptoms that have been commonly associated with COVID-19 (see **Appendix 3** in the Master Protocol, LDOS-21-001) with the capability of adding individualized symptoms not appearing in the common list. Daily ratings of perceived incapacity will also be obtained to assess the overall impact of symptoms on participant’s day-to-day functionality, using the 11–point NRS with a range from “No Limitation” to “Extreme Limitation." At the conclusion of their participation, participants will also report on their global impression of therapeutic change using an established 7–point scale (PGIC), their belief regarding active v. placebo group assignment, and their qualitative impressions of their illness experience elicited through narrative probes. Participants will be oriented to and trained on the use of these PRO instruments to ensure comprehensibility and usability, in accordance with recent FDA guidance for assessing COVID-19 in outpatient clinical trials. In addition to the above subjective measures, daily spO2 and body temperature ratings will be captured using Sponsor-provided pulse oximeter and thermometer, and recorded by participants.

2. STUDY DESIGN

2.1. Overall Design

This is a randomized double-blind placebo-controlled study in which patients newly-diagnosed with COVID-19, with symptoms of WHO Ordinal Scale levels ≤3, will be randomized in a 1:1 ratio to receive oral tablets/capsules of the study products, or placebo, in addition to the standard of care (SOC), for 5 days. Following this 5-day period, participants assigned to Group 1 will continue their famotidine QID treatment for an additional nine days. Those participants assigned to Group 22 will continue their famotidine-matching placebo QID administration for an additional nine days. The study will maintain equal distribution of male and female participants. There will be a subsequent follow-up period of 90 days from Baseline.

2.2. Scientific Rationale for Study Design

Rather than focusing on direct-acting antiviral drugs (a historically ineffective strategy for acute viral pneumonias (Ruuskanen O, 2011), we seek to identify and develop combinations of pharmaceutical agents with complementary mechanisms-of-action (MOA) that will mitigate the hyperinflammatory cascade triggered by SARS-CoV-2 infection. We propose that selection of pharmaceuticals, which target more specific mechanistic pathways involved in COVID-19 inflammation, will reduce off-target non-specific effects, which may complicate clinical management, reduce efficacy and increase treatment-emergent adverse events. The decades of experience in developing therapeutic drug cocktails for AIDS guides our strategy; optimal solutions typically require multiple drugs with complementary MOA.

This study is designed to test the efficacy and safety of combinations of two well-understood agents; famotidine and celecoxib. Each of these agents separately demonstrate clinical activity in mitigating COVID-19 disease symptoms or severity, and each of which appear to have separate and complementary mechanisms of action (MOA). The combination therapy will be assessed in patients hospitalized for moderate-to-severe COVID-19 (LDOS-21-001-01), and compared to matched placebo interventions to best elucidate the therapeutic value and safety of the two-component intervention. Data collection and entry will be optimized through an adaptive clinical data platform—[redacted]

2.3. Justification for Dose

A comprehensive review of dose justification is provided in **Section 2.2** of the Master Protocol (**LDOS-21-001**).

2.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow-up.

The end of the study is defined as the date of the last visit of the last participant in the study, or the last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial (Day 90). Thus, the last participant to complete their Day 90 Follow-up Visit will be considered Last Patient Last Visit (LPLV).

3. STUDY POPULATION

This study will enroll males and females aged 18 years or older that have tested positive with COVID-19, with a WHO grade that is ≤3. There is no restriction on a prospective participant's Body Mass Index (BMI) or previous COVID-19 vaccination status. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Study subjects will be recruited by social media, television, and radio advertisements that direct them to the study website (www.treatmycovid.com). These adverstisements are run in the market areas and states in which there are active clinical trial sites. Subjects should be literate and able to speak English in order to communicate with the professional staff involved in monitoring safety during the study and to complete the subject forms in [redacted] Individuals responding to recruitment messages will be instructed to contact the website or study call center phone number to receive further information.

Individuals will be informed that they will be compensated for blood draws ($50 for each blood draw) and for their continued follow-up visits at Days 30, 60, and 90 ($50 per visit). If subjects complete all required study visits, then their total compensation is $300; compensation is prorated by the number of visits successfully completed and will be paid at Day 90 whether or not the subject is still enrolled in the study at that time. Compensation will be provided to participants in the form of an electronic Visa or Mastercard giftcard, which will be sent to the participant's registered email address.

3.1. Screen Failures

Screen failures are defined in **Section 3.2** of the Master Protocol (**LDOS-21-001**). Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

3.2. Inclusion Criteria

1. Participant must be at least 18 years of age, inclusive, at the time of signing the informed consent
2. Confirmed SARS-CoV-2 PCR positive or positive by FDA-authorized at-home antigen test within 5 days of enrollment (i.e., signing the ICF), as shown by medical history and reported PCR or antigen test result; confirmatory PCR testing is required for participants with an antigen-positive test result before starting study medication
3. Reports having one or more symptoms consistent with SARS-CoV-2 (as defined in Appendix 3, Table 4 of the Master Protocol, LDOS-21-001)
4. COVID-19 Diagnosis must be WHO Grade ≤3,as referenced in Section 1.1, Table 2
5. Contraceptive use by men or women should be consistent with **Appendix 4** of the Master Protocol (**LDOS-21-001**).
6. Reliable access to the Internet via a browser installed on personal device or computer.
7. Capable of understanding and providing of signed informed consent

3.3. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Pregnancy or breastfeeding
2. Ongoing antiviral or antiretroviral treatment
3. Known history of HIV
4. Ongoing anti-inflammatory treatment that cannot be temporarily discontinued during the study. This includes nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids – including Dexamethasone (dexamethasone administration restricted to recommended standard of care use per NIH COVID-19 Guidelines)
    a. drugs dependent on gastric pH for absorption, e.g., dasatinib, delavirdine, mesylate, cefditoren, and fosamprenavir
    b. tizanidine (CYP1A2) substrate,
    c. drugs that interfere with hemostasis (e.g., warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]),
    d. angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta-blockers,
    e. diuretics,
    f. digoxin.
5. Ongoing treatment that cannot be temporarily discontinued during the study, with: antimalarials, antiarrhythmics, tricyclic antidepressants, natalizumab, quinolones, macrolides, agalsidase alfa and beta.
6. Ongoing famotidine or celecoxib or other COVID-19 clinical investigational treatment(s) within the past 30 days, or current participation in another investigational clinical trial.
7. History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
8. History of immunosuppression
9. Rejection of participation by Principal Investigator or Sponsor
10. Any contraindication for famotidine or celecoxib treatment:
    a. Famotidine or celecoxib hypersensitivity
    b. Retinopathy, visual field or visual acuity disturbances
    c. History of cardiovascular disease, such as congestive heart failure, QT prolongation, myocardial infarct, bradycardia (< 50 bpm), ventricular tachycardia, other arrhythmias
    d. Myasthenia gravis
    e. Psoriasis or porphyria
    f. History of renal failure/dialysis or a glomerular clearance <60 mL/min
    g. History of severe hypoglycemia
    h. Moderate or severe hepatic impairment, e.g., Child-Pugh Class B or C

i. Known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history or experience with other CYP2C9 substrates, such as warfarin and phenytoin.

3.4. Study Intervention(s) Administered

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo, intended to be administered to a study participant according to the study protocol. Study interventions are presented in Table 7, below.

Table 7: Study Interventions

ARM Name	**Group 1: Investigational + SOC**		**Group 2: Placebo + SOC**
Intervention Name	Famotidine	Celecoxib	Placebo
Type	Drug	Drug	Matching placebo
Dose Formulation	Tablet	Capsule	Matching tablets, or capsules, as applicable, to the investigational drug products.
Unit Dose Strength(s)	80 mg	400 mg (initial dose), then 200 mg	None
Dosage Level(s)	QID for 14 days	BID for 5 days	Matching placebo for famotidine QID for 14 days; matching placebo for celecoxib BID for 5 days; QD for 5 days
Route of Administration	Oral	Oral	Oral
Sourcing	Each of the study interventions will be supplied by the Sponsor, obtained from commercial sources, and, upon PI confirmation of eligibility, shipped directly to the study participant in pre-packaged dispensing units.		
Packaging and Labeling	Study Intervention will be provided in pre-packaged dispensing units. These will be labeled for investigational use, per FDA guidance.		
Alternative Name	Pepcid®	Celebrex®	N/A

3.5. Preparation/Handling/Storage/Accountability

1. Only participants enrolled in the study may receive and self-administer study medications. Prior to shipping to the study participant, all study medications must be

stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff. IP Prep/Handling /Storage and accountability will be the responsibility of the study medication shipper. The site investigator will be responsible for authorizing drug shipment to the participant, and will confirm their receipt of the shipment as well.

2. When study medications are taken, the study participant will enter confirmation on a daily basis into [redacted]. The study medication shipper will complete accountability with the study regime by reviewing and comparing against returned medications. These data will be entered into be reported via [redacted].
3. Further guidance and information for the final disposition of unused study medications are provided in the Manual of Operations.

3.6. Measures to Minimize Bias: Randomization and Blinding

Descriptions of randomization and blinding techniques are provided in **Section 4.2** in the Master Protocol (**LDOS-21-001**).

3.7. Study Intervention Compliance

The study medications taken by the participant are noted in [redacted] daily. The Investigator will periodically monitor study intervention use within [redacted], and council the participant if there is concern about compliance. Information pertaining to missed doses is provided in **Section 4.6** of the Master Protocol (**LDOS-21-001**).

3.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage instruction/prescription, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 1–3 days before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator, in consultation with the Medical Monitor.

3.8.1. Prohibited Concomitant Medication

The following concomitant medications will be prohibited during the course of the study:

- Aspirin

- CYP2C9 inhibitors, e.g., fluconazole, or inducers, e.g.. rifampin
- Dexamethasone – **NOTE:** Standard of care is permitted for all participants while they are participating in this outpatient study. Per the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, the panel recommends against the use of dexamethasone or other systemic glucocorticoids in the absence of another indication. Per NIH, there is currently a lack of safety and efficacy data on the use of these agents in outpatients, and they could potentially cause harm. If a participant needs to be hospitalized due to worsen COVID-19 symptoms and/or requires supplemental oxygen, then study medications are required to be stopped prior to the use of dexamethasone. These participants are considered clinical failures and will continue to be followed for outcome assessment.

3.8.2. Rescue Medicine

It is not anticipated that there would be need for rescue medication for these studies, as these are marketed medications that have been shown to be well-tolerated. In the case of an emergency, the participant should be monitored and supportive therapy should be employed, based on the judgment of medically trained personnel and the individual product labels. All rescue medications, including dosage, time of administration, and outcome are to be recorded in the [redacted] platform.

3.9. Dose Modification

Dose modification from the specified study regimens will be required if any of the following occur after the administration of study drugs:

- a participant's glomerular clearance (GFR) drops to <60 mL/min without developing QT prolongation or CNS AEs (i.e., delirium, hallucinations, disorientation, or seizures) after the results from their weekly laboratory results have been obtained by the investigator; or
- a QT wave prolongation is registered on their mobile ECG monitor; or
- a central nervous system (CNS) AE (i.e., delirium, hallucinations, disorientation, or seizures) is reported by the subject.

If any of the above occur, then the investigator will instruct the participant to stop all scheduled study medications.

For those participants with a drop in GFR and no QT prolongation or CNS AEs, they may resume study medications after testing demonstrates the GFR is >60 mL/min. Upon resolution, study drugs can be added back in stepwise fashion, e.g., BID, then TID, and finally QID. All missed or withheld doses will be noted in [redacted]

For participants that had a QT prolongation or CNS AE (i.e., delirium, hallucinations, disorientation, or seizures), study medication will be permanently stopped and they will be followed for safety for the remainder of their study participation (Day 90).

3.10. Intervention after the End of the Study

After study completion, study participant will be instructed to contact their personal physician to address any health-related issues.

4. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

4.1. Discontinuation of Study Intervention

Discontinuation of study intervention and participant discontinuation/withdrawal are addressed in the Master Protocol (**LDOS-21-001**).

4.2. Participant Discontinuation/Withdrawal from the Study

A discussion of participant discontinuation or withdrawal from the study is provided in **Section 5** of the Master protocol (**LDOS-21-001**).

4.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fail to enter their daily impressions via [redacted] and are unable to be contacted by the Investigator or designee.

The following actions will be taken if a participant fails to participate, as above:

- The Investigator or designee must attempt to contact the participant and counsel the participant on the importance of complying with the study conditions, and ascertain whether or not the participant wishes to and/or should continue in the study. All contact attempts and outcomes must be documented. Information regarding specific processes regarding contact of unresponsive participants can be found in the Manual of Procedures.

Information pertaining to study and site closure is addressed in **Section 8.1.9** of the Master Protocol.

5. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 5). Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 5.

Regulatory, Ethical and Study Oversight Considerations are provided in **Appendix 1** of the Master Protocol.

5.1. Screening

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened, and to confirm eligibility or record reasons for screening failure, as applicable. All participants will be consented prior to any study-specific tasks or tests being asked of the participant. Once consented, and the Investigator reviews Screening information to verify that the patient is eligible, they will be randomized to study group in [redacted]

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 5.

The following will be performed/collected during screening:

- Informed consent
- Inclusion and Exclusion criteria, including confirmation of positive COVID-19 infection by PCR test & confirmation of negative pregnancy test for child-bearing females by self-administered pregnancy test provided to participant
- Demographics
- Medical History (within the last 3 years, including relevant events not to exceed 5 years) and body weight reporting
- Concomitant medication review
- Comprehensive metabolic panel via a mobile phlebotomy and laboratory service provider (Sponsor-contracted)
- Nasal swab for confirmatory PCR testing for those participants prescreened with only a positive at-home antigen test via a mobile phlebotomy and laboratory service provider (Sponsor-contracted)
- Randomization and initiation of drug shipment

5.2. Baseline and Enrollment

Adherence to the study design requirements, including those specified in the SoA, is essential, and required for study conduct.

The following will be performed/collected at Baseline/Day 1:

- Concomitant medication review
- Review of reported baseline symptoms
- Confirmation of Study Drug Receipt & Initial Dose
- Adverse Event Review
- Participant Symptom, SpO2, mobile ECG, & Temperature reporting

Eligibility to continue with dosing of study drug will be confirmed by the Investigator, at Baseline. Should a participant be found to have become ineligible at this time, it will be noted in [redacted] and the participant discontinued from the study as a Screen failure.

5.3. Treatment Period

Participants will take their daily study treatment regimen from Day 1 through Day 14 and will log into [redacted] whether they took their study medication and time taken and record SpO2 reading, temperature, and symptoms and severity. On Days 7 (± 1 day) and 14 (± 1 day), participants will conduct a mobile ECG and will have a comprehensive metabolic panel blood draw performed to ensure GFR is >60 mL/min and other safety values are within acceptable ranges as determined by the investigator. The blood draw is conducted via a mobile phlebotomy and laboratory service through the Sponsor; laboratory values will be available in [redacted] for investigator review.

5.4. Follow-up

The follow-up period will consist of virtual participant self-reporting of current symptoms, SpO2, and temperature via the [redacted] platform, until they reach Day 90.

5.5. Efficacy Assessments

Determination of efficacy of the combination therapy, relative to placebo, will be determined as described in Section 1.4.

5.6. Safety Assessments

The study participants will provide daily self-assessments of symptom progression, using the [redacted] platform. Body temperature, SpO2, and pulse will be measured and recorded by the participant daily, using Sponsor-provided thermometers and pulse oximeters, respectively. The study participants will perform a mobile ECG on Days 7 (± 1 day) and 14 (± 1 day) with the reads performed by the investigators, who will follow up with the participant.

Should the symptoms reported by the participant go outside of the normal ranges, severity, or expected condition, [redacted] will trigger an alert to the site for the investigator to review for AEs/follow-up.

5.6.1. Demographic/Medical History

Participants will self-report demographic and medical history information through the [redacted] platform.

5.6.2. Physical Examinations

No physical examinations will be conducted for this study.

5.6.3. Clinical Safety Laboratory Assessments

There will be mobile clinical laboratory samples taken and assessed for safety during this study. All subjects will have baseline and weekly comprehensive metabolic panels performed through Day 14 to assess eGFR and other hepatic and safety parameters.

5.6.4. Suicidal Ideation and Behavior Risk Monitoring

Based on the long history of the use of these medications, there is no expectation that there is an increased risk of suicidal ideation or behavior.

5.7. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in **Appendix 2** of the Master Protocol (**LDOS-21-001**). CNS-related AEs including confusion, delirium, hallucinations, disorientation, agitation, seizures, and lethargy will be captured in the eCRF as an AE of special interest (AESI).

5.7.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be reported from the start of study interventions (Baseline) until the end of the follow-up period, at the time points specified in the SoA (Table 5). Medical occurrences that begin after obtaining informed consent, but before the start of study intervention will be recorded in the Medical History/Current Medical Conditions field in [redacted] not in the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in **Appendix 2** of the Master Protocol (**LDOS-21-001**). The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor. It is expected that, after the completion of the Follow-up period, that the study participant will be instructed to contact their personal physician to report any adverse events they may experience.

5.7.2. Recording, Evaluating, and Assessment of AEs/SAEs

The method of recording, evaluating, and assessing causality and relationship to study drug of AE and SAE and the procedures for completing and transmitting SAE reports are provided in **Appendix 2** of the Master Protocol (**LDOS-21-001**). Care will be taken not to introduce bias

when detecting AEs and/or SAEs. Open-ended and non-leading [redacted] screen prompts is the preferred method to inquire about AE occurrences.

5.7.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent contacts. All Seawall be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 4.3). Further information on follow-up procedures is given in **Appendix 2** of the Master Protocol (**LDOS-21-001**).

5.7.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify the FDA authority about the safety of a study intervention under clinical investigation. The Sponsor will comply with specific regulatory requirements relating to safety reporting to the regulatory authority (for example, the filing of a Form 3500A and/or Annual Safety Report under the applicable IND), Institutional Review Boards (IRBs) and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to applicable regulatory requirements and Sponsor policy, and forwarded to Investigators, as necessary.
- An Investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

5.7.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the end of the follow-up period.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in **Appendix 4** of the Master Protocol (**LDOS-21-001**).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

5.7.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Disease-related events (DREs) are addressed **Section 6.2.6** in the Master Protocol (**LDOS-21-001**).

5.8. Treatment of Overdose

Recommendations with regard to treatment of overdose are provided in **Section 6.3** of the Master Protocol (**LDOS-21-001**)

5.9. Pharmacokinetics/Pharmacodynamics

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study.

6. EXPLORATORY ENDPOINTS

6.1. Exploratory Endpoints: Tracking participants' self-assessments on multiple dimensions.

Patient Recorded Outcomes (PRO) for symptom severity: Participants will select personally relevant COVID-19 symptoms from a list and track the severity of each on a daily basis before and after start of treatment using an 11–point NRS ranging from "None" to "Extreme". After 15 days, participants will continue to complete brief daily and weekly diaries for a total of 3 months following first day of treatment. The list of symptoms will initially contain typical COVID-19 symptoms but will enable participants to add other symptoms that emerge that they attribute to their illness.

Endpoints: The presence, severity and duration of COVID-19 signs and symptoms. Specific metrics include assessing the slope, time course, and extent of change in the mean severity score of various subsets of endorsed symptoms from prior to onset of treatment to specified post-treatment days (e.g., Days 3, 7, 11, 15) and to specified clinical milestones (e.g., sustained clinical recovery).

Hypotheses: The patient population consists of recently PCR-tested individuals who have begun to show one or more cardinal symptoms of COVID-19. Based on published epidemiological surveys the symptoms experienced by outpatients will typically persist over about 4–8 days, with some participants showing an initial period of symptom escalation, and another subset experiencing deterioration of their clinical status around day 7–15, potentially requiring hospitalization. Moreover, a significant minority of participants will report some degree of enduring symptoms over the course of the ensuing weeks to months. We hypothesize that the daily trend following treatment will differ between the treatment groups and the placebo group with a faster and steeper decline in symptom severity scores after treatment and with significantly greater proportional improvement across symptoms with treatment than with placebo. We hypothesize that any early trend towards increasing severity will invert sooner following treatment than with placebo. We hypothesize that the 7–day AUC of symptom severity scores post treatment for key symptoms pertaining to everyday performance (difficulty breathing, myalgia and fatigue) will differ significantly and by more than 50% between treatment and placebo groups.

Purpose: To demonstrate the utility of participants' self-assessed symptom severity ratings to measure the degree and time course of clinical improvement and differentiate between treatment and controls groups.

PRO for impact of illness on performance: Participants will respond daily to three functional queries, on an 11–point NRS ranging from "No Limitations" to "Extreme Limitations", tracked daily before and after start of treatment. The three discrete dimensions of impact of treatment on capability to perform are: impaired ability to perform my essential tasks and duties; impaired ability to care for myself without assistance, and impaired ability to assist others.

Endpoints: The presence, extent and duration of COVID-19-related functional impairments. Specific metrics include assessing the slope, time course, and extent of change in the three impairment scores from prior to onset of treatment to specified post-treatment days (e.g., Days 3, 7, 11, 15) and to specified clinical milestones (e.g., sustained clinical recovery).

Hypotheses: We hypothesize that the daily trend following treatment will differ between the treatment and placebo groups with a quicker and steeper decline in functional impairment scores with significantly greater proportional improvement with treatment v. placebo (the treatment group will improve faster than the control group). We hypothesize that any existing trend towards increasing functional impairment will invert earlier following treatment than with placebo. We hypothesize that the 7–day AUC of functional impairment scores post treatment will differ significantly and by more than 50% between treatment and placebo groups.

Purpose: To demonstrate the utility of participants' self-assessed impairment ratings in capturing the degree and time course of improved real-world performance and differentiate between treatment and control groups.

6.2. Participant Protocol Debrief: Participants will respond to a trio of probes.

1. Participants will generate retrospective assessments of their overall degree of improvement at Day 15 following onset of treatment and at termination of participation using the PGIC (Patient's Global Impression of Change) scale, an established, widely-used 7-point qualitative rating scale of perceived treatment efficacy ("very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse.").

   Endpoint: The perceived presence or absence of overall clinical improvement.

   Hypothesis: The treatment groups will score higher on the PGIC than the placebo group.

2. Participants will respond to the following prompt at the conclusion of their participation: "I believe I received: 1) an investigational drug, or 2) a placebo".

   Endpoint: Effectiveness of blinding provisions.

   Hypothesis: At least 20% of participants will not correctly select treatment.

   Purpose: to explore the degree of awareness/ perception of participants to the impact of treatment.

3. Participants will be given the option of selecting a short narrative that best describes their own individual outcome from a pool of alternatives ("sum-ups"), as well as the option of composing an open-ended narrative account.

   Endpoints: Qualitative information/insights extracted from participant's accounts describing the personal significance of their treatment experience.

   Hypothesis: Participant descriptions of disease and treatment will reveal the patient point of view on efficacy and aspects of the treatment that matter to them.

   Purpose: In accordance with FDA's PFDD principles, to learn what aspects of disease and treatment matter most to patients.

7. STATISTICAL CONSIDERATIONS

7.1. Statistical Hypotheses

The following statistical hypotheses will be tested in a hierarchical manner:

H_{01}: pFCI - pP = 0

H_{11}: pFCI - pP < 0

H_{02}: pFC - pP = 0

H_{12}: pFC - pP < 0

where pFCI represents the proportion of participants with at least one COVID-19–related medically attended contact, due to increased symptom severity, or death due to COVID-19 rate through Day 30 for the famotidine/celecoxib combination, pFC represents the relative frequency of the same parameter for the famotidine/celecoxib combination, and pP the relative frequency for placebo.

7.2. Sample Size Determination

The sample size was estimated assuming that an interim analysis with stopping criteria for futility will be performed after 50% of participants have a primary endpoint assessment at Day 30. The O'Brien-Fleming beta-spending function is used to determine the non-binding futility boundary.

A total of 1318 evaluable participants, defined as part of the Full Analysis population (659 per group) are required to detect a relative reduction in the primary efficacy parameter of 60% in the active treatment arms compared to placebo (from of 6% in the placebo group to 2.4% in the active groups) with 90.0% power and using a two-sided χ^2-test with 0.5% significance level, assuming variances are pooled, and that continuity correction was not used. Assuming a 10% screen failure rate, 1465 enrolled participants will be required.

7.3. Populations for Analyses

For purposes of analysis, populations are defined in Table 8.

Table 8: Analysis Populations

Population	Description
Enrolled	All participants that have signed the Informed Consent Form, met the eligibility criteria, were randomized to study intervention, discontinued before first intake (Screening failures) **or** received at least one of study medication (Intent-To-Treat (ITT), Safety)
Full Analysis (FAS)	All participants who were randomized and received at least one dose of study medication. Participants in the FAS/ITT will be analyzed as randomized.

Population	Description
Per Protocol (PP)	All participants who were included in the ITT, completed at least the 30-day assessments, and had no major protocol deviations that could have an influence on the primary efficacy endpoint. Participants in the PPS will be analyzed as treated.
Safety	All participants randomly assigned to study intervention and who take at least one dose of study intervention. Participants will be analyzed according to the intervention they actually received.

Participants excluded from the analysis sets mentioned above will be determined during the Blinded Data Review (BDR) and reasons for exclusions will be documented in the BDR report.

7.4. Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock of the interim analysis and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints considering all relevant aspects of the FDA Guidance for Industry (E9) Statistical Principles for Clinical Trials (FDA Guidance for Industry E9 Statistical Principles for Clinical Trials, 1998).

7.4.1. Demographics and Baseline Characteristics

Disposition, demographics, medical history, prior/concomitant medication, and compliance will be displayed in a descriptive manner. Further details will be provided in the SAP.

7.4.2. Efficacy Analyses

The **primary efficacy** endpoint, the percentage of patients with at least one COVID-19–related medically attended contact, due to increased symptom severity or death (all-cause mortality) through Day 30, will be analyzed using a two group χ^2 test with pooled variances and no continuity correction. Statistics and the associated 95% confidence interval will be provided. The primary efficacy analysis will be performed using the ITT and will be repeated for robustness purposes with the PP.

In case of missing data of the primary endpoint at day 30 (Visit 4), the primary analysis will consider participants (with missing primary endpoint data until day 30) as having at least one medically attended visit. For sensitivity purposes, the primary efficacy analysis will be repeated by excluding participants with missing primary endpoint until day 30 (Complete Case Analysis).

The **secondary safety endpoints**: Incidence of Related Serious Adverse Events (SAE), Incidence of discontinuation due to related SAE and Incidence of death will also be analyzed using a χ^2 test. Descriptive statistics including exploratory confidence intervals/p-values will be provided.

All **other efficacy endpoints** will be analyzed in an exploratory manner by applying appropriate statistical methods (e.g. χ^2 test for incidences, log rank test and Kaplan Meier method for cumulative incidences, ANOVA for continuous variables) using the FAS set. Descriptive statistics including exploratory confidence intervals/p-values will be delivered.

All **other safety related endpoints** will be analyzed in a descriptive way by providing descriptive statistics and/or shift tables from baseline to the assessment visits.

For more details of the statistical analysis, methods/models refer to the SAP.

7.4.3. Interim Analyses

An interim analysis with stopping criteria for futility and validation of sample size is planned after 50% of the participants have completed the primary endpoint assessment at Day 30 (Visit 4).

To prevent power loss due to this interim analysis, a beta-spending function was used to calculate stopping bound according to O'Brien and Fleming (Lan, 1983) (O'Brien, 1979). The futility bound for difference in proportions between active treatments and placebo is 0.0232 in the interim analysis. The nominal level of significance is not affected α=0.05 (two-sided) and 90% power is kept for the final analysis. The interim analysis will be performed on the Full Analysis set.

If the primary endpoint is missing at Day 30, the participant will be excluded from the interim analysis (Complete Case Analysis). The interim efficacy analysis will be performed using a two-group chi-square test comparing the FCI combination with placebo followed by the FC–placebo comparison.

If the study is not stopped due to futility after the interim look, the assumptions for the sample size determination will be checked and the sample size may be increased if a decrease in treatment difference by more than 10% (due to a lower placebo rate and/or due to a higher rate in the active arms) is observed.

The SAP will describe the planned interim analyses in greater detail.

7.4.4. Independent Data Safety Monitoring Board (DSMB)

The DSMB activities are described in **Section 7.1.1** of the Master Protocol (**LDOS-21-001**). The delivered information will contain un-blinded information and will therefore be prepared by an unblinded statistician team from the CRO ([redacted] The same team will perform the interim analysis but will not be involved in the final analysis. The information provided via those listings must be limited to DSMB members and will not be shared with any other personnel involved in the conduct or analysis of the study.

8. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

8.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with appropriate principles of patient protection, as detailed in the **Section 8.1.1**of the Master Protocol (**LDOS-21-001**).

8.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, as requested, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to FDA. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

8.1.3. Informed Consent Process

- The informed consent process for this study will be entirely virtual and done via phone call between the participant and site investigator. No in-person consenting will be performed.
- Upon initiating contact with the study staff, the prospective participant will be contacted by the site Investigator via phone call. The participant will be advised by the Investigator \on the nature of the study, and answer all questions regarding the study. If the prospective participant is deemed potentially qualified, the Informed Consent will be administered.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The participant will sign the informed consent using [redacted] an electronic method that will capture the electronic signature of the participant and the PI..The authorized person administering the informed consent must also sign the ICF.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

8.2. Appendix 2: Data Management

For this study, a secure, adaptive, interactive data collection platform, [redacted] will be used. Because the platform is web-enabled, it provides a means for real-time data entry by the participantthrough any device that can access the internet. The participant is able to enter their ratings of symptom status and impact, and will be provide choices in drop-down menus, which evolve, based on prior responses.

8.2.1. Data Protection

Data protection considerations are provided in **Section 8.1.4** of the Master Protocol (**LDOS-21-001**).

8.2.2. Dissemination of Clinical Study Data

Clinical study data dissemination is addressed in **Section 8.1.6** of the Master Protocol (**LDOS-21-001**).

8.2.3. Data Quality Assurance

Data quality assurance is addressed in **Section 8.1.7** of the Master Protocol (**LDOS-21-001**).

8.2.4. Source Documents

Information pertaining to source documents, including definition, is addressed in **Section 8.1.8** of the Master Protocol (**LDOS-21-001**).

8.2.5. Study and Site Closure

Study and site closure is addressed in Section 8.1.9 of the Master Protocol (**LDOS-21-001**).

8.2.6. Publication Policy

Guidelines pertaining to publication of study results are detailed in **Section 8.1.10** of the Master Protocol (**LDOS-21-001**).

8.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

A detailed overview of Adverse Event information is provided in **Appendix 2** of the Master Protocol (**LDOS-21-001**).

8.4. Appendix 4: Self-Rating of Symptoms and Symptom Scoring

A detailed overview of [redacted]-based self-rating of symptoms and symptom scoring is provided in **Appendix 3** of the Master Protocol (**LDOS-21-001**).

8.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

A detailed overview of Contraceptive Guidance and Collection of Pregnancy information is provided in **Appendix 4** of the Master Protocol (**LDOS-21-001**).

9. REFERENCES

FDA Guidance for Industry E9 Statistical Principles for Clinical Trials. (1998). FDA.

Lan, K. a. (1983). Discrete sequential boundaries for clinical trials. *Biometrika, 70*, 659-663.

O'Brien, P. a. (1979). A Multiple Testing Procedure for Clinical Trials. *Biometrics, 35*, 549–556. doi:10.2307/2530245

Ruuskanen O, L. E. (2011). Viral pneumonia. *Lancet, 377*(9773), 1264-1275.

1.

2. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/.