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| Title of Study: | Safety, tolerability, and treatment effect of belnacasan in patients with COVID-19: A proof of concept, randomized, double-blind, placebo-controlled trial of orally administered belnacasan tablets for the treatment of mild to moderate COVID-19 |
| NCT #: | NCT05164120 |
| Date: | December 23, 2021 |

| **Safety, tolerability, and treatment effect of belnacasan in patients with COVID-19**<br>A proof of concept, randomized, double-blind, placebo-controlled trial of orally administered belnacasan tablets for the treatment of mild to moderate COVID-19 | |
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| Clinical Trial Protocol | |
| **Name of product** | Belnacasan (VX-765/RVT-201/MSR-001) |
| **Phase** | 2 / Proof of Concept |
| **Protocol Number** | MedStar-COVID-19-belnacasan-2001 |
| **IND Number** | 155290 |
| **Sponsor** | MedStar Health |
| **Protocol Authors** | Alexander Kroemer, MD<br>Email: alexander.h.kroemer@medstar.net<br>Office: 202-444-4052 \| Cell: 202-830-7371<br><br>Khalid Khan, MD<br>Email: khalid.m.khan@medstar.net<br>Office: 202-444-6047 \| Cell: 202-805-4289<br><br>Thomas M. Fishbein, MD<br>Email: thomas.m.fishbein@medstar.net<br>Office: 202-444-6396 \| Cell: 202-316-3487 |
| **Clinical Trial Protocol Version / Date** | 2.2 / December 23, 2021 |
| **Protocol Amendment Number / Date** | NA |



**CONFIDENTIALITY STATEMENT**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| 9-POS | 9-Point Ordinal Disease Severity Scale |
| ADL | Activities of daily living |
| AE | Adverse event |
| ALC | Absolute lymphocyte count |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| CFR | Code of Federal Regulations |
| CRF | Case report form |
| CRP | C-reactive protein |
| CS | Clinically significant |
| CT | Computed tomography |
| COVID-19 | Coronavirus disease 2019 |
| CTCAE | Common terminology criteria for adverse events |
| CXR | Chest x-ray |
| DLT | Dose limiting toxicity |
| DSMB | Data and safety monitoring board |
| ECMO | Extracorporeal membrane oxygenation |
| EDC | Electronic data capture |
| EKG | Electrocardiogram |
| ET | Early termination |
| FDA | Food and Drug Administration |
| G-CSF | Granulocyte colony-stimulating factor |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Heart rate |
| I/E | Inclusion/Exclusion |
| ICH | International Council for Harmonization |
| IDS | Investigational Drug Services |
| IND | Investigational New Drug |

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|---|---|
| IP | Investigational product (belnacasan or placebo) |
| IRB | Institutional review board |
| LAR | Legally authorized representative |
| LDH | Lactate dehydrogenase |
| LOC | Level of consciousness |
| NCS | Not clinically significant |
| PE | Physical examination |
| P-gp | P-glycoprotein |
| QID | Four times a day |
| RP | MedStar Health Research Pharmacy |
| RR | Respiratory rate |
| RT-PCR | Reverse transcriptase polymerase chain reaction |
| SAE | Serious adverse events |
| SAP | Statistical analysis plan |
| SARS | Severe acute respiratory syndrome |
| SBP | Systolic blood pressure |
| SOC | Standard of care |
| $SpO_2$ | Peripheral capillary oxygen saturation |
| TID | Three times a day |
| TNF-α | Tumor necrosis factor alpha |
| WHC | Washington Hospital Center |
| WHO | World Health Organization |

## SUMMARY OF CHANGES FROM PROTOCOL VERSION 2.1 TO 2.2

1. *Initial Date and Completion Date changed in the **Study Synopsis** to November 2021 and April 2022, respectively.*
2. *Version date updated on the title page and footer of Protocol.*
3. *Revision to **Section 5.1 Study Description** allowing PCR confirmation by a home health agency with virtual and e-consent practices stating, "Some patients identified will require a PCR-confirmed COVID test, having only had a rapid antigen test. Patients requiring a PCR test can either have one collected with screening labs prior to leaving the MedStar enrollment site or have these labs collected via a home-health research visit. Prior to study-specific procedures the study team will obtain their consent in-person or remotely. An e-consent platform, Interlace, can also be used to consent potential subjects via electronic platform. Once their COVID-19 status is confirmed via PCR they will complete the remainder of their screening/enrollment visit at at either MedStar Washington Hospital Center or MedStar Franklin Square within the next 1 to 3 days. Virtual consent or e-consent will follow MedStar institutional policies and procedures." Under **Background of Care** adding that individuals will additionally be screened from Urgent Cares. Addition of Urgent Care under **Study Population** and home health PCR. Under **Recruitment Methods** describing MedStar process, methods and materials that will be used to identify and recruit potential subjects.*
4. *Revision to **Section 5.2, Table 1 Schedule of Events superscript 3** with addition of home health agency option to collect RT-PCR sample in the subjects' home in the event their initial testing did not include PCR, to ensure expeditious resulting and appropriate inclusion in the trial. Clarification made that subjects will return to a MedStar site for completion of the screening/enrollment visit 1 to 3 days following confirmation. **Superscript 12** also updated to indicate laboratory tests collected at the screening/enrollment visit may be collected by a home health agency in the subjects' home.*
5. *Revision to **Section 5.2, Table 1 Schedule of Events superscript 6** adding detail that outside laboratories will result certain labs, with locations included as part of Appendix 12, 12.1 Labs and Tests. Specifically, CD3+ counts/cell isolation/storage for future use samples and markers of inflammation will be sent to respective laboratories.*
6. *Revision to **Section 5.2, Table 1 Schedule of Events superscript 4** adding detail of pregnancy testing schedule*
7. *Revision to **Section 5.2, Table 1 Schedule of Events superscript 13 a**dding clarification to chest x-ray and chest CT requirement.*
8. *Revision to **Section 6.1** clarifying that the screening/enrollment visit may occur over more than one day if confirmatory PCR testing is needed.*
9. *Revision to **Section 7.1** adding description of virtual consent or e-consent practices and communications and operations flow with the home health agency and the subject.*
10. *Revision to **Section 7.5** clarifying initial screening will be at a MedStar site or via home health.*

11. *Revision to **Sections 10.1 through 10.4** clarifying remote and in-person consent as well as documentation of consent and e-consent.*
12. *Addition of Troponin I, High Sensitivity (hs-TnI) to chemistry labs in **Appendix 12, 12.1 Labs and Tests** given myocardial organ involvement is an endpoint to be monitored throughout the trial (5 of 5).*

## SUMMARY OF CHANGES FROM PROTOCOL VERSION 2.0 TO 2.1

1. ***Table 1: Schedule of Events****, the Subjects section was revised to clarify that the "subject will report via telephone to study team at Day 42 & 60 their temperature, SpO2 resting, and symptom tracking. Diary completion for the subject ends at Day 28."*
2. *Per request of the reviewing Institutional Review Board, the following clarification was added as a footnote to* ***Section 5.2 Study Assessments, Table 1: Schedule of Assessments****, "[12]These laboratory tests will be collected at a one-time blood draw at each visit, a total of 5 collections at the 5 visits (Screening, Day 7, Day 14, Day 21, and Day 28). The amount drawn at each timepoint is as follows: Screening visit (56 mL or 11 teaspoons), Day 7 (44 mL or 9 teaspoons), Day 14 (56 mL or 11 teaspoons), Day 21 (20 mL or 4 teaspoons), and Day 28 (48 mL or 10 teaspoons). The early termination visit would be in lieu of one of the in-person visits, it is not included in the total." The IRB requested that the number of blood draws, the timepoints for collection, and the volume collected be added."*

## SUMMARY OF CHANGES FROM PROTOCOL VERSION 1.0 TO 2.0

### *1. Exclusion Criteria*

The exclusion criteria related to liver function, which appears in the Synopsis as well as Sections 5.3 and 7.5 has been changed to "*Elevated liver function tests (determined by ALT, AST, GGT, or ALP > 2 x upper limit of normal,* ***and/or*** *total Bilirubin > upper limit of normal).*"

### *2. Laboratory Abnormalities*

Additional text has been added to Section 7.7 that reads as follows:

"*Particular attention will be paid to determine the possibility of drug induced liver injury (DILI) as detailed in the FDA guidance document "Drug-Induced Liver Injury: Premarketing Clinical Evaluation." Liver tests (ALT, AST, ALP, and total Bilirubin) will be performed at enrollment and at days 7, 14, and 28 throughout the drug administration period. For patients exhibiting signs of liver disease such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash, extensive laboratory testing will be performed that includes above liver chemistries immediately. Otherwise, on routine weekly testing an increase of serum aminotransferase levels to >3x upper limit of normal would automatically trigger repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and total Bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. If symptoms and/or aminotransferase levels remain >3x upper limit of normal, the participant will be monitored more closely with lab schedule, in-person or virtual evaluation twice weekly or more. A thorough evaluation for additional causes of liver test anomalies will be conducted in consultation with Hepatology. A case report form page will be created and DSMB review triggered. Otherwise, discontinuation of treatment will be considered immediately if:*

- *ALT or AST >8x upper limit of normal*
- *ALT or AST >5x upper limit of normal for more than 2 weeks*
- *ALT or AST >3x upper limit of normal and total Bilirubin >2x upper limit of normal or INR >1.5*
- *ALT or AST >3x upper limit of normal with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).*"

### *3. Serious Adverse Events*

The definition of Serious Adverse Events, which appears in Section 7.9, has been updated to read:

*"**Serious Adverse Event:** An untoward event or reaction that at any dose:*

- *results in death*
- *is life-threatening*
- *results in hospitalization or prolongs existing hospitalization*
- *results in permanent or significant disability or incapacity*
- *requires intervention to prevent permanent impairment/damage*
- *results in congenital anomaly or birth defect*

*In addition, any important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."*

***4. Stopping Rules***

The study stopping rules, which appear in the Synopsis as well as Sections 4, 7.15, and 8.4 have been changed to "*should two or more subjects develop a similar Grade 3 SAE that is at least possibly related to belnacasan or should one or more subjects develop a ≥ Grade 4 SAE that is at least possibly related to belnacasan, the trial will be paused for DSMB safety review*."

**STUDY SYNOPSIS**

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| **Study Title** | **Safety, tolerability, and treatment effect of belnacasan in patients with COVID-19**: A phase 2, proof of concept, randomized, double-blind, placebo-controlled trial of orally administered belnacasan tablets for the treatment of mild to moderate COVID-19 |
| **Protocol Number** | MedStar-COVID-19-belnacasan-2001 |
| **Study Phase** | 2 / Proof of Concept |
| **Methodology** | This study is conducted as a proof of concept safety, tolerability and treatment effect Phase 2 trial in subjects with confirmed SARS-CoV-2 infection and mild to moderate COVID-19.<br>In this hypothesis generating, randomized, double-blind, placebo-controlled trial, 20 subjects will be given 900 mg TID of belnacasan and 20 subjects will be given a placebo TID. Belnacasan or placebo will be given for 28 days and assessments of safety, tolerability, and treatment effect will be performed for 60 days. Subjects in both |

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| | treatment arms will also be treated with the background standard of care that is at that time appropriate and commensurate with their COVID-19 disease severity.<br>Subjects will use a diary to record study drug intake as well as symptoms and activity levels; assess physical parameters using a study-provided thermometer and pulse oximeter; be assessed at regular intervals by the Study Team via the telephone and in-person follow-up clinic visits at MedStar Washington Hospital Center or MedStar Franklin Square Medical Center; and give blood for laboratory tests. A Data Safety & Monitoring Board (DSMB) will be engaged throughout for data monitoring and safety evaluation. |
| **Study Duration** | Subjects will be in the study for 60 days. The study will last 3-6 months. |
| **Study Centers** | This study will be conducted at MedStar Washington Hospital Center (WHC) and/or MedStar Franklin Square and/or other MedStar hospital and/or urgent care sites. |
| **Objectives** | The purpose of this trial is to assess the safety, tolerability and treatment effect of the orally administered Caspase-1 inhibitor, belnacasan, for the treatment of patients with mild to moderate COVID-19 and to generate hypotheses for future trials.<br>**Primary Objective**: To determine the ***safety and tolerability*** of belnacasan (VX-765/RVT-201/MSR-001) administered orally for 28 days in subjects with mild to moderate COVID-19 as determined by ***Adverse Events and Serious Adverse Events***.<br>**Secondary Objective**: To generate data on the ***treatment effect*** of belnacasan (VX-765/RVT-201/MSR-001) administered orally for 28 days in subjects with mild to moderate COVID-19 as determined by its ***effect size*** on outcomes in five areas:<br>1. Clinical recovery and resolution of COVID-19 symptoms<br>2. Physical functions and parameters relevant to COVID-19<br>3. COVID-19 related deterioration and mortality<br>4. WHO 9-point ordinal scale for clinical improvement<br>5. Surrogate markers of COVID-19-related inflammation and organ involvement<br>The hypothesized end result of treatment with belnacasan would be to reduce the symptomatic and clinical burden, length of disease course, and disease progression of COVID-19. |
| **Number of Subjects** | The intent is to enroll 40 subjects to participate in a 1:1 allocation in this randomized, double-blind, placebo-controlled safety, tolerability and treatment effect trial. |
| **Study Description** | A Phase 2, proof of concept randomized, double-blind, placebo-controlled trial of orally administered belnacasan tablets for the treatment of mild to moderate COVID-19. Belnacasan or placebo will be administered for 28 days and follow-up will occur for 60 days, alongside background standard of care. |
| **Study Population** | Subjects with an RT-PCR assay confirmed SARS-CoV-2 infection and mild to moderate COVID-19 at time of enrollment. |
| **Study Drug Administration** | Oral, three times per day as per protocol. |

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| **Inclusion / Exclusion Criteria** | The study population is defined as subjects who meet the following criteria:<br>**Inclusion Criteria:**<br>• Subject (or legally authorized representative) provides written informed consent prior to the initiation of any study procedures.<br>• Subject understands and agrees to comply with planned study procedures, including using the diary.<br>• Subject agrees to the collection of nasopharyngeal swabs and venous blood per protocol.<br>• Subject is male or non-pregnant female adult ≥18 years of age at time of consent.<br>o Women with a history of menstruation must agree to use two methods of contraception, at least one of which is highly effective, for the duration of the study as well as to undergo additional pregnancy testing during the study.<br>• Subject has a laboratory confirmed SARS-CoV-2 infection as determined by RT-PCR assay prior to enrollment.<br>• Subject has evidence of either mild or moderate COVID-19 illness of less than 7 days from first onset, with minimal baseline symptom severity based on patient-reported FDA scoring system defined as follows:<br>o Subject presents with **at least two** common symptoms of COVID-19 from the following list: stuffy or runny nose, sore throat, cough, low energy or tiredness, muscle or body ache, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, shortness of breath with exertion (without supplemental oxygen requirement) with a score of 2 or higher; impairment in sense of smell or taste with a score of 1 or higher **OR**<br>o Subject presents with **any** (i.e., at least one) symptom of COVID-19 as defined above **AND** clinical evidence of moderate COVID-19 as defined by FDA guidance for industry (such as respiratory rate >20 breaths per minute, heart rate >90 beats per minute, with oxygen saturation >93% on room air at sea level).<br>• Subject presents with high-risk for COVID-19-related inflammation determined by at least one comorbidity, including obesity, diabetes, hypertension, stable heart disease, respiratory disease, and / or non-severe fatty liver disease.<br>• Subject's overall health condition is deemed as suitable to fully and safely participate in this trial as determined by the Investigator.<br><br>**Exclusion Criteria**<br>• Any clinical signs indicative of severe or critical COVID-19 as defined by FDA guidance for Industry at the time, including SpO2 < 93% *and / or* oxygen requirement.<br>• Hospitalization for COVID-19, or consideration thereof.<br>• ICU level of care and / or non-mechanical / mechanical ventilation *and / or* oxygen supplementation at time of enrollment.<br>• Pregnant or breast-feeding subjects.<br>• Subjects who cannot swallow tablets.<br>• History of any pre-existing organ impairment, such as: |

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| | ○ Severe kidney disease (known or estimated GFR <30 mL / minute) or on dialysis.<br>○ Uncontrolled, clinically significant heart diseases such as arrhythmias, angina or heart failure as defined by AHA / ACC Grade C and D.<br>○ Chronic respiratory disease requiring supplemental oxygen.<br>○ Moderate and severe hepatic impairment as defined by Child-Pugh scoring Class B and Class C<br>• Elevated liver function tests (determined by ALT, AST, GGT, or ALP >2 x upper limit of normal, and/or total Bilirubin > upper limit of normal).<br>• History of malignancy or immunodeficiency within the prior 5 years.<br>• Acute respiratory illness other than COVID-19.<br>• Active bacterial, viral or fungal infection (including HIV, hepatitis B, hepatitis C).<br>• While dosed with the IP, the taking of prohibited concomitant medication or the ingestion of food that interferes with the IP, including:<br>○ Non-COVID19-related anti-viral medication such as lopinavir, ritonavir, ribavirin or interferon-1β.<br>○ Systemically administered immunosuppressive and anti-inflammatory agents, other than background standard of care for COVID-19 at the time.<br>○ Drugs and foods that are potent inhibitors or inducers of CYP3A4 and / or P-gp, as listed in FDA "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers", (including herbal medications such as St. John's Wort) within 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug.<br>• Any other diseases or medical conditions or concomitant medications that are deemed as not compatible or appropriate for the subject's ability to fully and safely participate in this trial as determined by the Investigator. |
| **Study Product, Dose, Route, Regimen** | 40 subjects will participate in this randomized, double-blind, placebo-controlled safety, tolerability and treatment effect trial. In a 1:1 allocation, 20 subjects will receive 900 mg (three tablets each containing 300 mg) TID of orally administered belnacasan and 20 subjects will receive placebo tablets (three placebo tablets) TID, whereby randomization will be determined via a randomization table. |
| **Study Endpoints** | **Primary Endpoint:**<br>Incidence of Adverse Events and Serious Adverse Events assessed out to day 60.<br>**Secondary Endpoints:**<br>Secondary endpoints relate to generating data on the ***treatment effect*** of belnacasan as determined by its ***effect size*** on outcomes in five areas:<br>**1. Clinical recovery and resolution of COVID-19 symptoms**<br>***1a. Sustained recovery and resolution rates of common COVID-19 symptoms:*** (i.e., stuffy or runny nose, sore throat, cough, low energy or tiredness, muscle or body ache, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, shortness of breath with exertion; impairment in sense of smell or taste) |

Proportion of subjects in treatment group versus placebo group, respectively, who per symptom questionnaire on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization have achieved for two consecutive days:

- scores not higher than 0 for all symptoms
- scores not higher than 1 for all symptoms
- scores not higher than 0 for all symptoms *other than* impairment of taste or smell
- scores not higher than 1 for all symptoms *other than* impairment of taste or smell

***1b. Sustained improvement of global impression rates:*** Proportion of subjects in treatment group versus placebo group, respectively, who per symptom questionnaire on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization have answered for two consecutive days

- "Yes" to "*In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?*"
- "Yes" to "*In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?*"
- "None" to "*In the past 24 hours, what was the severity of your overall COVID-19 related symptoms at their worst?*"
- "Mild" to "*In the past 24 hours, what was the severity of your overall COVID-19 related symptoms at their worst?*"

***1c. Time to sustained recovery, resolution or improvement:*** comparison in treatment group versus placebo group, respectively of the number of days from randomization to the first day of achieving each item in 1a and 1b above.

**2. Physical functions and parameters relevant to COVID-19**

***2a. Parameter rates:*** Proportion of subjects in treatment group versus placebo group, respectively, who on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization per thermometer or pulse oximeter reading experienced:

- fever at any point between enrollment and day 2 post randomization and who were afebrile <38C
- oxygenation of SpO2>=96% or >93% in room air when resting

***2b. Time to and length of parameters:*** comparison in treatment group versus placebo group, respectively of the number of days

- from randomization to the first day of achieving sustained (i.e., at least 2 days) resolution of fever for subjects who presented with fever at any point between enrollment and day 2 post randomization
- with temperature <38C or >=38C experienced in total during the first 28 days post randomization
- from randomization to the first day post randomization of achieving oxygenation of SpO2>=96% in room air when resting for subjects who presented with SpO2>93% and <96% in room air, when resting, at enrollment
- with oxygenation of SpO2>= 96% or SpO2>93% in room air, when resting, in total during the first 28 days post randomization

**3. COVID-19 related deterioration and mortality**

***3a. Deterioration and mortality rates:*** Proportion of treatment group, versus placebo group, respectively, who per subject reporting or medical records by day 14, day 28 and by day 60 post randomization had experienced:

- an emergency department visit, other than at study enrollment or study visits
- hospitalization for COVID-19
- hospitalization for COVID-19 requiring oxygen
- hospitalization for COVID-19 requiring ICU
- hospitalization for COVID-19 requiring ventilation
- COVID-19 related death
- death
- hospitalization or death

***3b. Time to and length of deterioration***: Comparison of treatment group versus placebo group, respectively, in the number of days

- from randomization until the first day of experiencing hospitalization for COVID-19
- of hospitalization for COVID-19 experienced in total by day 14, by day 28 and by day 60 post randomization
- of hospitalization for COVID-19 requiring oxygen experienced in total by day 14, by day 28 and by day 60 post randomization
- of hospitalization for COVID-19 requiring ICU experienced in total by day 14, by day 28 and by day 60 post randomization
- of hospitalization for COVID-19 requiring ventilation experienced in total by day 14, by day 28 and by day 60 post randomization

**4. WHO 9-Point Ordinal Scale**

0. Uninfected or "no clinical or virological evidence of infection"
   - defined as subject answering "Yes" to "*In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?*"
1. Not hospitalized, no limitations on activities
   - defined as subject answering "Yes" to "*In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?*"
2. Not hospitalized, limitation on activities
   - defined as subject answering "No" to "*In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?*"
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
6. Hospitalized, intubated
7. Hospitalized, advanced life support including invasive mechanical ventilation or ECMO
8. Death

***4a) Ordinal scale rates:*** proportion of treatment group versus placebo group, respectively who had experienced:

- an improvement from scale 2 at randomization to scale 1 or 0 on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization,
- an improvement from scale 1 at randomization to scale 0 on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization
- a sustainment from scale 1 at randomization to scale 1 on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization

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| | ○ any improvement of the scale (i.e., at least a 1-point decrease) between enrollment and days 7, 14, 28, 42, 60 post randomization<br>○ any worsening of the scale (i.e., at least a 1-point increase) between enrollment and days 7, 14, 28, 42, 60 post randomization<br>○ scale 4 or higher by day 28 or day 60 post randomization<br>○ scale 6 or higher by day 28 or day 60 post randomization<br><br>***4b) Ordinal scale averages, highs, and lows:*** Comparison of treatment group versus placebo group, respectively, at days 14, 28 and 60 post randomization in the<br>○ average of daily scale value on that day<br>○ overall average of daily scale value experienced since enrollment<br>○ in the worst (i.e., highest) daily scale value experienced since enrollment<br>○ in the best (i.e., lowest) daily scale value experienced since enrollment<br><br>***4c) Time to improvement:*** Comparison of treatment group versus placebo group, respectively, in the number of days from enrollment until first experiencing a 1-point improvement sustained over at least 2 days by day 14, day 28 and by day 60 post randomization<br><br>***4d) Length of ordinal scale experience:*** Comparison of treatment group versus placebo group, respectively, in the total number of days by day 14, day 28 and by day 60 post randomization on which subjects experienced a given scale value (i.e., 3, 4, 5, 6, 7)<br><br>**5. Surrogate markers of COVID-19-related inflammation and organ involvement**<br><br>***5a) Analysis and comparison of*** surrogate markers of COVID-19 related inflammation and organ involvement as determined by biochemistry, hematology, and immunology labs and studies, in treatment group versus placebo group, respectively, for<br>○ values on days 1 (enrollment), 7, 14, 21, 28 post randomization<br>○ changes from enrollment to days 7, 14, 21, or 28 post randomization<br>○ changes between days 7, 14, 21, 28 post randomization<br><br>***5b) Reference range rates****:* proportion of treatment group versus placebo group, respectively, who experience normal / in-range values for a given marker at days 7, 14, 21, 28 post randomization |

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| **Statistical Considerations** | **Study Populations:**<br>• ***Safety & Tolerability Population***: All enrolled subjects who have received at least 1 dose of IP (belnacasan or placebo) will be studied. Even if subjects have discontinued study treatment, as long as they maintain consent, they will continue to be in the study and included in analysis, i.e., their safety and tolerability information will continue to be collected for at least 60 days.<br>• ***Treatment Effect Evaluable Populations***: All enrolled subjects who have received at least 1 dose of IP (belnacasan or placebo) will be studied. Even if subjects have discontinued study treatment, as long as they maintain consent, they will continue to be in the study and included in analysis, i.e., their outcome information will continue to be collected for at least 60 days.<br>**Analysis Methods:**<br>FDA Data Standard Guidelines will be followed. Continuous variables will be summarized using the number of observations, number of observations above the limit of quantification (if applicable), mean, standard deviation (SD) median, and range. Categorical variables will be summarized using frequency counts and percentages. Comparison of belnacasan and placebo groups will utilize Poisson regression for counts, Cox proportional hazards regression for time-to-event data and mixed effects models for continuous and categorical data obtained over study days.<br>**Primary Safety and Tolerability Analysis:**<br>All safety & tolerability analyses will be performed on the Safety Population. The safety data will be presented in individual listings and summary tables. Overall safety will be assessed by the number of belnacasan dosed subjects experiencing a grade 4 or 5 SAE during the trial. Of 20 subjects enrolled in the belnacasan group, 3 or more developing grade 4 or 5 SAE probably related to belnacasan would be considered unlikely due to chance. Therefore, belnacasan will be determined safe if no more than 2 subjects develop a grade 4 or 5 SAE in the belnacasan group probably related to belnacasan.<br>In terms of stopping rules, should two or more subjects develop a similar Grade 3 SAE that is at least possibly related to belnacasan or should one or more subjects develop a ≥ Grade 4 SAE that is at least possibly related to belnacasan, the trial will be paused for DSMB safety review.<br>**Secondary Treatment Effect Endpoint Analysis:**<br>Event counts over 60 days will be analyzed by Poisson regression. Time to events will be analyzed by Cox regression. Differences between belnacasan and placebo with respect to change in continuous endpoints will be assessed by mixed effects models for continuous repeated measures data and mixed effects logistic models for repeated categorical variables. Endpoint proportions of belnacasan and placebo groups will be assessed by contingency table analysis (chi-square).<br>**Sample Size Considerations:**<br>As this is a proof-of-concept study, it will likely not be powered to detect belnacasan – placebo differences that are clinically meaningful. For example, the observed difference in endpoint rate ratios would need to be over 60% to achieve 80% power with an alpha error rate of 5% for 20 subjects in each group. This study will provide an estimate of the belnacasan effect size to inform a larger trial where a more clinically meaningful difference can be detected. |
| **Initial Date** | November 2021 |
| **Completion Date** | April 2022 |

# 1 BACKGROUND, STUDY RATIONALE AND DOSING RATIONALE

## 1.1 Background and study rationale

For more than one year, coronavirus disease 2019 (COVID-19) – an acute respiratory disease caused by SARS-CoV-2 that also has profound multi-systemic inflammatory involvement – has cost countless lives and livelihoods, especially for vulnerable populations with comorbidities characterized by chronic inflammation. The full spectrum of COVID-19 ranges from asymptomatic, to a mild, self-limiting respiratory tract illness, to severe progressive pneumonia, multi-organ failure, and death [1]. Since its first discovery, the virus has continued to spread, even with attempted control with a variety of public health measures. There are more than 36 million cases in the United States, accounting for a quarter of the worlds documented cases, and over 620,000 deaths [2]. In general, there is likely an underestimate of total cases since the prevalence of asymptomatic carriers is yet unknown. What is clear, is that individuals at highest risk are those over 65 years and / or those with concomitant chronic conditions most notably hypertension, diabetes, pre-diabetes, obesity, chronic cardiorespiratory disorders and chronic renal and liver impairment [1, 3-6]. While there are racial disparities in the greater number of Black and Hispanic patients experiencing a more severe course there is no evidence that this is related to anything other than underlying comorbidities and socioeconomic factors, often limiting their ability to socially distance.

There have been promising scientific breakthroughs for preventing and treating severe COVID-19, including via vaccines, monoclonal antibody and steroid treatments. However, there is to-date no targeted treatment for SARS-CoV-2-mediated inflammation and subsequent complications in COVID-19. In general drug treatments aimed at the virus have so far not lived up to their promise. Most notably the nucleotide analog remdesivir was demonstrated to mitigate the course of the illness when given early in the course [7]. Subsequent data however failed to show a benefit. While antibody for treatment has been available the uptake of this therapy has been limited by parenteral administration. While efficacious in patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease [8], monoclonal antibodies (e.g., bamlanivimab, casirivimab, and imdevimab) are costly and their administration is complicated for outpatients and providers as it is given intravenously, in an hour long infusion that must take place in a separate unit since recipients are infectious. A late 2020 report from the Department of Health and Human Services found that only 5-20% of available supply had been used. Currently the most widely accepted and

available treatment is dexamethasone having shown a clear benefit in seriously affected, hospitalized patients [9].

The most hopeful remedy for the population at large is vaccination and at this time vaccines from three sources (Pfizer/BioNTech, Moderna, Johnson & Johnson) have been authorized for emergency use in the United States after having demonstrated the ability to prevent disease in up to 95% of individuals [10]. However, vaccines may not be sufficient to address COVID-19 across the US population for four reasons. First, vaccine hesitancy persists (https://aspe.hhs.gov/pdf-report/vaccine-hesitancy). Second, vaccination may only confer immunity for a limited number of months, necessitating the need for booster shots (https://www.cnbc.com/2021/04/21/scientist-who-helped-develop-pfizer-biontech-covid-vaccine-agrees-third-shot-is-needed-as-immunity-wanes.html), which may not be taken, or taken on time, by all who need them. Third, immunocompromised people, such as transplant recipients on immunosuppressive medication, have recently been shown to not develop sufficient antibodies through vaccination [11, 12]. Fourth, it remains to be seen to what extent vaccines are effective against emerging new variants with immune-escape properties [13-15], especially the delta variant.

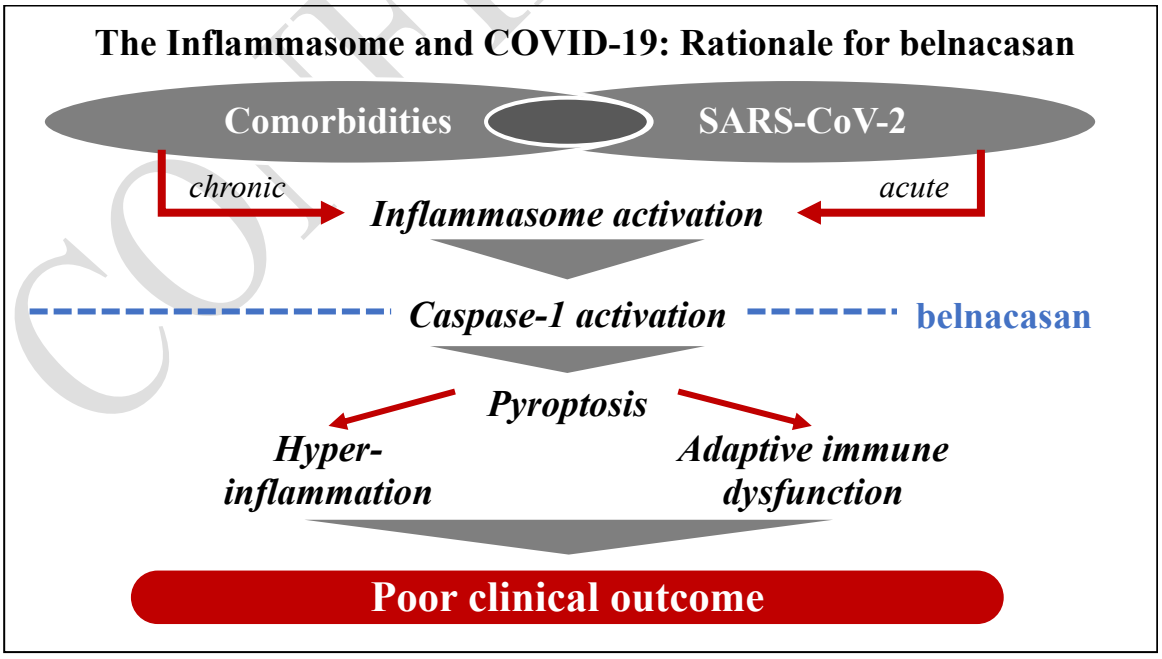
Moreover, given that even mild COVID-19 cases can result in devastating, likely inflammatory-driven, persisting effects (https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html), there is clearly an unmet need for a therapeutic option, especially an oral one, that can mitigate harmful uncontrolled inflammation and dysfunctional immune responses during a SARS-CoV-2 infection.

Fortunately, over the past year there has been better understanding of the immunologic pathophysiology of COVID-19, which in later stages is driven primarily by host immune responses to the virus [16]. In the spring of 2020, our team was the first to publish data linking the inflammasome / caspase-1 / pyroptosis axis to heightened pro-inflammatory IL-18 levels, lymphopenia and poor outcome in COVID-19 patients [6]. Over the summer of 2020, a Brazilian study in over 100 patients expanded our findings, and also showed direct evidence of NLRP3 inflammasome activation and caspase-1 mediated pyroptosis in SARS-CoV-2-infected monocytes *in vitro*, as well as in blood and lung tissue of COVID-19 patients [17, 18]. Inflammasome formation, as evidenced by expression of caspase-1 and NLRP3 in leukocytes and endothelial cells, was also found in the lungs of patients with fatal COVID-19 pneumonia [19, 20]. Most recently, several studies further corroborated and expanded these findings by showing that SARS-

CoV-2 infects monocytes and directly activates the inflammasome / caspase-1 / pyroptosis axis leading to pro-inflammatory cell death and cytokine release [21, 22]. Importantly, it was further demonstrated that a caspase-1 specific inhibitor was effective in blocking pyroptotic cell death of SARS-CoV-2-infected monocytes and subsequent release of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α [21]. In addition, from a mechanistic standpoint, it was recently shown that SARS-CoV-2 viroporin encoded by ORF3a activates the NLRP3 inflammasome and caspase-1 via potassium efflux [23]. Moreover, key ORF3a amino acid residues required for inflammasome activation were found to be conserved in virus isolates across continents, highlighting the universality of this inflammatory pathway [23].

Taken together, a growing body of evidence demonstrates that upstream SARS-CoV-2-mediated inflammasome and caspase-1 activation leading to pyroptosis, trigger uncontrolled hyper-inflammation via cytokine release (IL-18, IL-1β, IL-6, and TNF-α) as well as immune dysfunction of monocytes and lymphocytes downstream [16, 24-28]. Moreover, activation of the inflammasome / caspase-1 / pyroptosis axis could also explain COVID-19 related organ damage and tissue pathology of the heart, kidney, lungs, liver, pancreas and nervous systems, as it has been shown that SARS-CoV-2 also appears to cause pyroptosis in a variety of other cell types, including lung pneumocytes and endothelial cells in these organs [27-32].

**Illustration 1**



Based on this growing body of evidence, this trial proposes that the orally-administered belnacasan, which following hydrolysis on contact with water is a highly specific caspase-1 inhibitor (also known as IL-1β converting enzyme) upstream of pyroptosis and pro-inflammatory cytokine release, is a much more targeted and potentially safer alternative to current generalized anti-inflammatory COVID-19 treatments such as corticosteroids, especially for comorbid patients with an already chronically-activated inflammasome [6, 25, 27, 28, 33-36] (Illustration 1).

### 1.2 Belnacasan (VX-765/RVT-201/MSR-001)

The drug substance has a molecular formula of $C_{24}N_{33}CIN_4O_6$ and has molecular weight of 509.0 and comes as a tablet preparation. It is hydrolyzed on contact with water to an active form and is a caspase-1 inhibitor (caspase-1 is also known as IL-1β converting enzyme). Blocking this enzyme with belnacasan (VX-765/RVT-201/MSR-001) has been shown to prevent production of IL-1β, IL-18, and pyroptosis in healthy and disease states. The drug has been extensively developed originally by Vertex Pharma and more recently Roivant Sciences but currently has no FDA or IND approved usage for any indication.

### 1.3 Dosing rationale

Belnacasan (VX-765/RVT-201/MSR-001) has previously been studied in rodents and large animals including dogs and monkeys to doses of up to 2000mg/kg/day for toxicity studies in dogs. Dosing at these levels and in multi-dosing schedules have not shown any severe and particularly life-threatening side effects. In human trials, including for conditions such as seizure disorders, the drug has been trialed in increments of 300mg/dose on a TID or QID regimen up to 900mg QID for 13 weeks, in nearly 100 patients.

Detailed pharmacokinetic studies from Vertex / Roivant are available for review. In brief, ex-*vivo* studies have demonstrated that Lipopolysaccharide stimulated IL-1β production is 50% suppressed by the active metabolite of belnacasan at a concentration of 0.8mcg/ml. This translated in to 50% suppression of IL-1β by single oral dose of 400mg while 80% suppression was achieved with doses of 800 and 1600mg. There was gradual but marked inhibition of IL-18 over 14 days in healthy controls as compared to placebo and 60% inhibition with 900mg TID as well as 1200mg TID and 1800mg TID during the duration of the study. For this study we have therefore chosen our primary dose as 900mg TID in the absence of data on acute viral infection / COVID-19.

The drug has previously been manufactured with appropriate due diligence in tablet form at 300mg/tablet (Data available from Roivant Sciences) and will be manufactured by the same compounding pharmacy (Metrics), in the original format for immediate use in this trial.

For this trial we will treat for a maximum of 28 days. Our rationale for this timeframe is that while there is an expectation that the illness lasts up to 12-15 days in those who recover without complication, others will endure a longer duration, and some will experience persistent, new onset or worsening disease related symptoms. A recent study from the Centers for Disease Control and Prevention (https://www.cdc.gov/mmwr/volumes/70/wr/mm7017e3.htm?s_cid=mm7017e3_w) found that among 3,171 non-hospitalized adult COVID-19 patients, 69% had one or more outpatient visits 28–180 days after the diagnosis. Two thirds had a visit for a new primary diagnosis, and approximately one third had a new specialist visit. Symptoms potentially related to COVID-19 were common new visit diagnoses. Visits for these symptoms decreased after 60 days but for some patients continued through 120–180 day. Furthermore, some individuals develop sequela that are likely related to post-viral immune dysregulation in the first few months albeit there is little known about this group. Though we are unlikely to learn about the effect of the drug in this latter population we do need to establish safety for a duration that includes the other groups mentioned above.

### 1.4 Brief summary of known systemic safety profile of belnacasan (VX-765/RVT-201/MSR-001)

Based on files held by Vertex and Roivant Sciences, which contains evidence from animal and human studies, there is no indication that belnacasan (VX-765/RVT-201/MSR-001) causes severe or life-threatening side effects. The only preclinical finding on toxicity studies was a reduction of the heart rate in dogs at 2000mg/kg/day, a dose that was estimated to be 10-25 times higher than the maximum in this study (900mg QID). In humans with epilepsy the drug has been used at dosages of 3600mg/day for up to 13 weeks. Adverse effects reported in humans were headache, dizziness, nausea and vomiting, abdominal discomfort and rash. Seizure was reported in more than one patient in one study on epilepsy.

### 1.5 Ongoing clinical studies with belnacasan (VX-765/RVT-201/MSR-001)

None, that have been declared by Roivant Sciences or evident on an extensive web search.

## 2 SUMMARY

In modern history there is been no greater health threat to life and livelihood than COVID-19, especially in the United States. While progress is being made to find treatments, there are potential drawbacks to all options. First, even with the prospect of vaccines being successful, there is a likelihood that patients with co-morbid conditions will likely suffer a protracted illness at least; that it will take time for the vaccine and any needed boosters to reach critical mass in the population, especially in the face of vaccine hesitancy; and that vaccines might not always be effective, especially as new virus strands and variants continue to emerge and early data show that immunosuppressed patients may struggle to develop anti-bodies. Second, while the most frequently heralded therapeutic of remdesivir offers the potential for earlier clearance of the virus, the inflammatory cascade results in continued need for inpatient and especially intensive care in high-risk patients. Furthermore, as an IV drug, the treatment itself requires inpatient treatment and likely needs specific timing to be optimally effective. Third, the prospect of immunosuppression, for example with a broad therapy such as dexamethasone or other equivalent corticosteroid, affects the inflammatory cascade but any use beyond a few days carries risks and therefore disadvantages that we believe will come to light with greater use of the drug and scrutiny of outcomes going forward. Over the next 12 months it is reasonable to expect that a large part of the United States population will undergo vaccination with the majority of these individuals being afforded some immunity for what is yet an undetermined length of time. What is clear however is that this form of coronavirus is likely to be around for the foreseeable future and though fewer people will be at risk for COVID-19, an effective treatment is necessary. While antiviral treatment may have an effect, it is clear from the pathophysiology that clearing virus may not be enough and such specific therapies to mitigate the individual's inflammatory response is important to reduce morbidity and mortality. **We believe that what is needed is an immunologically targeted medication that can be taken orally - and without the prospect of major immunosuppression in at-risk patients - and that can even be taken for early treatment in high-risk patients**. Based on the data presented here we believe that belnacasan (VX-765/RVT-201/MSR-001) may fulfil this role.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Primary Objective

To determine the ***safety and tolerability*** of belnacasan (VX-765/RVT-201/MSR-001) administered orally for 28 days in subjects with mild to moderate COVID-19 as determined by ***Adverse Events and Serious Adverse Events***.

## 3.2 Primary Endpoint

Incidence of Adverse Events and Serious Adverse Events assessed out to day 60.

## 3.3 Secondary Objective

To generate data on the ***treatment effect*** of belnacasan (VX-765/RVT-201/MSR-001) administered orally for 28 days in subjects with mild to moderate COVID-19 as determined by its ***effect size*** on outcomes in five areas:

1. Clinical recovery and resolution of COVID-19 symptoms
2. Physical functions and parameters relevant to COVID-19
3. COVID-19 related deterioration and mortality
4. WHO 9-point ordinal scale for clinical improvement
5. Surrogate markers of COVID-19-related inflammation and organ involvement

The hypothesized end result of treatment with belnacasan would be to reduce the symptomatic and clinical burden, length of disease course, and disease progression of COVID-19.

## 3.4 Secondary Endpoints

**1. Clinical recovery and resolution of COVID-19 symptoms**

***1a. Sustained recovery and resolution rates of common COVID-19 symptoms:***
(i.e., stuffy or runny nose, sore throat, cough, low energy or tiredness, muscle or body ache, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, shortness of breath with exertion; impairment in sense of smell or taste)

Proportion of subjects in treatment group versus placebo group, respectively, who per symptom questionnaire on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization have achieved for two consecutive days:

- scores not higher than 0 for all symptoms
- scores not higher than 1 for all symptoms
- scores not higher than 0 for all symptoms *other than* impairment of taste or smell
- scores not higher than 1 for all symptoms *other than* impairment of taste or smell

***1b. Sustained improvement of global impression rates:*** Proportion of subjects in treatment group versus placebo group, respectively, who per symptom questionnaire on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization have answered for two consecutive days

- "Yes" to "*In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?*"
- "Yes" to "*In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?*"
- "None" to "*In the past 24 hours, what was the severity of your overall COVID-19 related symptoms at their worst?*"
- "Mild" to "*In the past 24 hours, what was the severity of your overall COVID-19 related symptoms at their worst?*"

***1c. Time to sustained recovery, resolution or improvement:*** comparison in treatment group versus placebo group, respectively of the number of days from randomization to the first day of achieving each item in 1a and 1b above.

**2. Physical functions and parameters relevant to COVID-19**

***2a. Parameter rates:*** Proportion of subjects in treatment group versus placebo group, respectively, who on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization per thermometer or pulse oximeter reading experienced:

- fever at any point between enrollment and day 2 post randomization and who were afebrile <38C
- oxygenation of SpO2>=96% or >93% in room air when resting

***2b. Time to and length of parameters:*** comparison in treatment group versus placebo group, respectively of the number of days

- from randomization to the first day of achieving sustained (i.e., at least 2 days) resolution of fever for subjects who presented with fever at any point between enrollment and day 2 post randomization

- with temperature <38C or >=38C experienced in total during the first 28 days post randomization
- from randomization to the first day post randomization of achieving oxygenation of SpO2>=96% in room air when resting for subjects who presented with SpO2>93% and <96% in room air, when resting, at enrollment
- with oxygenation of SpO2>= 96% or SpO2>93% in room air, when resting, in total during the first 28 days post randomization

**3. COVID-19 related deterioration and mortality**

***3a. Deterioration and mortality rates:*** Proportion of treatment group, versus placebo group, respectively, who per subject reporting or medical records by day 14, day 28 and by day 60 post randomization had experienced:

- an emergency department visit, other than at study enrollment or study visits
- hospitalization for COVID-19
- hospitalization for COVID-19 requiring oxygen
- hospitalization for COVID-19 requiring ICU
- hospitalization for COVID-19 requiring ventilation
- COVID-19 related death
- death
- hospitalization or death

***3b. Time to and length of deterioration***: Comparison of treatment group versus placebo group, respectively, in the number of days

- from randomization until the first day of experiencing hospitalization for COVID-19
- of hospitalization for COVID-19 experienced in total by day 14, by day 28 and by day 60 post randomization
- of hospitalization for COVID-19 requiring oxygen experienced in total by day 14, by day 28 and by day 60 post randomization
- of hospitalization for COVID-19 requiring ICU experienced in total by day 14, by day 28 and by day 60 post randomization
- of hospitalization for COVID-19 requiring ventilation experienced in total by day 14, by day 28 and by day 60 post randomization

**4. WHO 9-Point Ordinal Scale**

0. Uninfected or "no clinical or virological evidence of infection"
    a. defined as subject answering "Yes" to "*In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?*"
1. Not hospitalized, no limitations on activities
    a. defined as subject answering "Yes" to "*In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?*"
2. Not hospitalized, limitation on activities
    a. defined as subject answering "No" to "*In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?*"
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
6. Hospitalized, intubated
7. Hospitalized, advanced life support including invasive mechanical ventilation or ECMO
8. Death

***4a) Ordinal scale rates:*** proportion of treatment group versus placebo group, respectively who had experienced:

- an improvement from scale 2 at randomization to scale 1 or 0 on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization,
- an improvement from scale 1 at randomization to scale 0 on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization
- a sustainment from scale 1 at randomization to scale 1 on days 4, 7, 10, 14, 21, 28, 42, 60 post randomization
- any improvement of the scale (i.e., at least a 1-point decrease) between enrollment and days 7, 14, 28, 42, 60 post randomization
- any worsening of the scale (i.e., at least a 1-point increase) between enrollment and days 7, 14, 28, 42, 60 post randomization
- scale 4 or higher by day 28 or day 60 post randomization
- scale 6 or higher by day 28 or day 60 post randomization

***4b) Ordinal scale averages, highs, and lows:*** Comparison of treatment group versus placebo group, respectively, at days 14, 28 and 60 post randomization in the

- average of daily scale value on that day
- overall average of daily scale value experienced since enrollment
- in the worst (i.e., highest) daily scale value experienced since enrollment
- in the best (i.e., lowest) daily scale value experienced since enrollment

***4c) Time to improvement:*** Comparison of treatment group versus placebo group, respectively, in the number of days from enrollment until first experiencing a 1-point improvement sustained over at least 2 days by day 14, day 28 and by day 60 post randomization

***4d) Length of ordinal scale experience:*** Comparison of treatment group versus placebo group, respectively, in the total number of days by day 14, day 28 and by day 60 post randomization on which subjects experienced a given scale value (i.e., 3, 4, 5, 6, 7)

**5. Surrogate markers of COVID-19-related inflammation and organ involvement**

*Heart*: troponin; *Kidney*: creatinine, blood urea nitrogen (BUN), electrolytes (calcium, carbon dioxide, chloride, potassium, sodium, magnesium); *Pancreas*: glucose, HbA1c, lipase; *Liver*: ALT, AST, ALP, total bilirubin; *Muscle weakness*: creatinine kinase; *Hematology*: red blood cell count, hemoglobin, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), d-dimer; *Immunology*: white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, T cells, SARS-CoV-2 viral load in nasopharyngeal sample, SARS-CoV-2 serology in blood; *Inflammation*: CRP, ferritin, LDH, caspase-1, IL-18, IL-1β, IL-1 receptor antagonist, gasdermin D, IL-6, TNF-α, G-CSF

***5a) Analysis and comparison of*** surrogate markers of COVID-19 related inflammation and organ involvement as determined by biochemistry, hematology, and immunology labs and studies, in treatment group versus placebo group, respectively, for

- values on days 1 (enrollment), 7, 14, 21, 28 post randomization
- changes from enrollment to days 7, 14, 21, or 28 post randomization
- changes between days 7, 14, 21, 28 post randomization

***5b) Reference range rates****:* proportion of treatment group versus placebo group, respectively, who experience normal / in-range values for a given marker at days 7, 14, 21, 28 post randomization

# 4 SAFETY AND TOLERABILITY

The drug in an oral form has been used in nearly one hundred patients without a history of major side effects. During the trial, it is therefore anticipated that no more than 2 subjects out of 20 will have an adverse event of grade 4 or 5 that is probably related to belnacasan (VX-765/RVT-201/MSR-001). In terms of stopping rules, should two or more subjects develop a similar Grade 3 SAE that is at least possibly related to belnacasan or should one or more subjects develop a ≥ Grade 4 SAE that is at least possibly related to belnacasan, the trial will be paused for DSMB safety review. Safety Monitoring processes are identified in Section 7.14.

# 5 STUDY DESIGN

## 5.1 Study Description

This is a phase 2 proof of concept randomized, double-blind, placebo-controlled trial with the purpose of assessing the safety, tolerability and treatment effect of the orally administered Caspase-1 inhibitor, belnacasan, for the treatment of patients with mild to moderate COVID-19. 20 subjects will be given 900 mg TID of belnacasan and 20 subjects will be given a placebo TID for 28 days, and assessments of safety, tolerability, and treatment effect will be performed for up to 60 days.

At the screening / baseline / day 1 Visit, subjects will provide informed consent and be screened for eligibility based on the Inclusion / Exclusion criteria identified in Section 5.3. Subjects will also receive the first dose of study drug at this visit once study eligibility has been confirmed, and the second dose of study drug will be taken approximately 8-12 hours after the first dose. Study drug will be continued three times daily (morning, mid-day, and nighttime doses) through day 28. Some patients identified will require a PCR-confirmed COVID test, having only had a rapid antigen test. Patients requiring a PCR test can either have one collected with screening labs prior to leaving the MedStar enrollment site or have these labs collected via a home-health research visit at no cost to the potential participant. Prior to study-specific procedures the study team will obtain their consent in-person or by remote consent process. An e-consent platform, Interlace, may also be used to document consent electronically. Once their COVID-19 status is confirmed via PCR they will complete the remainder of their screening/enrollment visit at either MedStar Washington Hospital Center or MedStar Franklin Square within the next 1 to 3 days. The remote consent

process and e-consent will follow MedStar institutional policies and procedures (MG.O-004.06 and MG.O-004.07).

The trial duration will be approximately 60 days (8.5 weeks) for all subjects enrolled. As outlined in the Schedule of Events Table in Section 5.2, over the course of the study duration, all subjects will use a diary to record IP intake as well as symptoms and activity levels with guidance to do so at the same time each day; assess physical parameters using a study-provided thermometer and pulse oximeter for which detailed instructions will be provided at enrollment; be assessed at regular intervals by the Study Team via telephone calls and in-person follow-up clinic visits; and give blood for laboratory tests.

An experienced and appropriately licensed Study Team member will conduct the telephone study visits and be the point of contact if subjects experience deterioration, such as high temperatures (above 38C) or low oxygen saturation levels (below 93%). The primary coordinator of the trial will be a registered nurse, experienced in vital sign and symptom review, with the ability to escalate any medical concerns to the Principal Investigator as it relates to worsening of the subjects' illness or adverse event identification. The Principal Investigator or delegated Sub-Investigator, as documented on the study delegation log, is well-versed in delegation of appropriate tasks as defined by licensure and scope of practice and will work closely with the study team to assure delegation remains appropriate through the duration of the trial. Medical advice or direction will only be given by sufficiently licensed study personnel, either mid-level providers or physicians, in partnership with their primary care team.

Subjects will be instructed to fill in symptoms assessment, overall health assessment, temperature and oxygen saturation levels in the diary each morning; and to note in the diary 3 times per day that they have taken the study drug. The Study Team will conduct in-person visits with the subjects on days 7, 14, 21, and 28 and telephonic visits with subjects on days 1, 4, 10, 42, and 60; as well as when / if subjects contact them due to symptom deterioration as instructed. Subjects will receive reminders to complete the diary via text message and / or email. Subjects who prematurely discontinue study drug for any reason will be asked to have an Early Termination (ET) visit the day the last study drug dose is administered; moreover, they will be encouraged to stay enrolled so that further safety and outcome information can be collected and analyzed.

All data collected by the Study Team and recorded by the subjects will be entered into the EDC per the schedule of events. OnCore, a Clinical Trial Management System in which subject visits

can be monitored as well as Case Report Forms developed, will be used for this trial. Subjects will be asked to hand in their subject diary during visits on days 7, 14, 21, and 28.

**Background Standard of Care**

All eligible subjects will receive background standard of care, however there are certain prohibited medications subjects cannot be given while dosed with the IP as outlined in Section 5.4. Background standard of care will be commensurate with disease severity and aligned to standards at the time of the trial. At present, standard of care includes vaccines, antiviral treatment with remdesivir, monoclonal antibodies against SARS-CoV-2, dexamethasone, supplemental oxygen, noninvasive and invasive ventilation, antibiotics, vasopressors, anti-coagulation and ECMO; but this may evolve over the coming months as new therapies or treatments come online including off-label use of other drugs.

Patients recruited to the study will not be asked to forgo background standard of care in any way. Recruitment will be based on inclusion and exclusion criteria and include individuals evaluated for suspected COVID-19 in a MedStar Urgent care or the Emergency Room setting, and triaged not to need in-hospital care. These individuals have the potential but not the likelihood for hospital admission with worsening COVID-19 disease progression. Current outpatient standard of care includes symptomatic treatment and this will not be altered to the point that analgesics and antipyretics will be held. Patients whose COVID-19 related illness deteriorates to the point that they need ambulatory medical care or hospitalization will remain in the study and medical care as determined by managing physicians will not be subverted in any manner as part of the study. Patient data collection as per study diary and study visits will be maintained for the minimum 60 days and study drug will be provided and monitored for compliance unless there is an indication for discontinuation of study drug, see section on drug discontinuation.

**Study Population**

Urgent Care or Emergency Department presenting subjects, who are not under immediate consideration for inpatient admission and with onset of at least one moderate COVID-19 symptom of less than 7 days, will be assessed for eligibility on the basis of a positive antigen test or reverse transcriptase polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample on presentation to a MedStar Urgent care or the Emergency Department facility. If only a rapid test is resulted, a home health research visit will be arranged, following consent, to obtain a confirmatory RT-PCR test with initial screening labs.

**Enrollment of Diverse Study Population**

Recognizing that COVID-19 disproportionately impacts racial and ethnic minorities, the study will seek to enroll a diverse patient population. For example, one of the main trial sites, MedStar Washington Hospital Center, is the largest hospital in the District of Columbia. Its primary service area includes 11 zip codes, most of which are the zip codes that make up Wards 5, 7, and 8. Minorities represent 58% of the population in DC overall, and 69%, 97%, and 96% of the population in Wards 5, 7, and 8, respectively. Three Metrobuses service the campus and MedStar provides free, wheelchair-accessible shuttle buses from two Metrorail stations. Moreover, subjects will receive financial support for travel to and from study visits.

Both in terms of COVID-19 presentation and clinical trial enrollment, communities of color have represented the vast majority of patients at WHC. Specifically, over the last 15 months, nearly 6,000 patients have presented at the WHC emergency department with COVID-19. Of the 97% from whom race / ethnicity data were recorded, 7% were White Non-Hispanic, 67% were Black or African American Non-Hispanic, 21% were Hispanic and 6% were Other (Asian, American Indian, Alaska Native, or more than one race or ethnicity). The MedStar system has enrolled 875 subjects into COVID-19 trials, 89% (781 subjects) at WHC. Of the 94% from whom race / ethnicity data were recorded, 21% were White Non-Hispanic, 47% were Black or African American Non-Hispanic, 24% were Hispanic and 8% were Other (Asian, American Indian, Alaska Native, or more than one race or ethnicity).

**Number of Subjects**

Approximately 40 subjects will be recruited at WHC and / or other MedStar hospital and / or critical / clinical care sites.

**Recruitment Methods**

A daily COVID-19 testing list is acquired from the laboratory network in the MedStar system and will be used for screening purposes. A designated central study coordinator will review the list and contact patients directly by phone. The same coordinator will also screen the EMR for COVID -19 patients being discharged from the ED in the past 24 hours at Franklin Square and Washington Hospital Center. A dedicated phone script will be used to recruit patients by phone. The consent will be emailed or provided through the e-consent platform, Interlace, and time allowed for the subject to review and for questions to be addressed. A dedicated homecare company will be available for home COVID-19 RT-PCR testing and screening blood draw if

needed. Completion of screening, randomization and enrollment will be at either MedStar Washington Hospital Center or MedStar Franklin Square. The patient will be required to attend the same center for all in-person follow-up visits and end of study visits.

## 5.2 Study Assessments

**Table 1: Schedule of Events: 🧍 = In-Person; ☎ = Telephone; 📄 = Subject Self-Tracking**

| Time Point (Days) | Screen / enroll | D1[9] | D4 | D7 | D10 | D14 | D21 | D28 | D42 | D60 | ET[10] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **STUDY TEAM** | | | | | | | | | | | |
| **Inclusion / Exclusion** | 🧍 | | | | | | | | | | |
| **Consent** | 🧍 | | | | | | | | | | |
| **Screening Tests[1, 12]** | 🧍 | | | | | 🧍 | | | | | |
| **Demographics** | 🧍 | | | | | | | | | | |
| **CXR or CT[13]** | 🧍 | | | | | | | | | | |
| **Physical Exam** | 🧍 | | | 🧍 | | 🧍 | 🧍 | 🧍 | | | 🧍 |
| **Vitals[2]** | 🧍 | | | 🧍 | | 🧍 | 🧍 | 🧍 | | | 🧍 |
| **EKG** | 🧍 | | | 🧍 | | 🧍 | 🧍 | 🧍 | | | 🧍 |
| **CoV-2 N/P[3]** | 🧍 | | | | | 🧍 | | 🧍 | | | 🧍 |
| **Standard labs[4, 12]** | 🧍 | | | 🧍 | | 🧍 | | 🧍 | | | 🧍 |
| **Blood draws[5, 12]** | 🧍 | | | 🧍 | | 🧍 | 🧍 | 🧍 | | | 🧍 |
| **Immunology tests[6, 12]** | 🧍 | | | 🧍 | | 🧍 | 🧍 | 🧍 | | | 🧍 |
| **CoV-2 blood[7, 12]** | | | | | | | | 🧍 | | | 🧍 |
| **AE assessment** | 🧍 | ☎ | ☎ | 🧍 | ☎ | 🧍 | 🧍 | 🧍 | ☎ | ☎ | 🧍 |
| **Symptoms assessment** | 🧍 | ☎ | ☎ | 🧍 | ☎ | 🧍 | 🧍 | 🧍 | ☎ | ☎ | 🧍 |
| **WHO 9-Point Scale[8]** | 🧍 | ☎ | ☎ | 🧍 | ☎ | 🧍 | 🧍 | 🧍 | ☎ | ☎ | 🧍 |
| **SUBJECTS** (as recorded in study diary) | | | | | | | | | | | |
| **IP/placebo intake** | | 📄 \| Three times per day through day 28 or ET..... | | | | | | | | | |
| **Temperature[11]** | | 📄 \| Daily via thermometer through day 28 or ET; subject will report via telephone to study team at Day 42 & 60 | | | | | | | | | |
| **SpO2 resting[11]** | | 📄 \| Daily via pulse oximeter through day 28 or ET; subject will report via telephone to study team at Day 42 & 60 | | | | | | | | | |
| **Symptom tracking** | | 📄 \| One time per day through day 28 or ET; subject will report via telephone to study team at Day 42 & 60 | | | | | | | | | |

[1]Screening tests: HIV, Hepatitis B, Hepatitis C, and pregnancy (serum pregnancy test for women of child-bearing potential per MedStar definition at enrollment and at day 14).

[2]Vital signs: oral temperature, heart rate, systolic blood pressure.

[3]Quantitative nasopharyngeal SARS-CoV-2 RNA testing (RT-PCR): nasopharyngeal or throat swabs will be used; any FDA-approved or commercial testing method will be acceptable. A home health agency may be used to confirm COVID-19 by RT-PCR in the subjects' home in the event their initial testing did not include PCR, to ensure expeditious resulting and appropriate inclusion into the trial. If home health is used to collect the PCR test or there is a delay in PCR resulting at initial screening, the subject will return to either MedStar Washington Hospital Center or MedStar Franklin Square for completion of the screening/enrollment visit in 1 to 3 days, once positive PCR is confirmed, to complete all study procedures including randomization and medication dosing under observation.[4]Standard labs: serum chemistry, coagulation tests and hematology. Pregnancy tests for women of childbearing potential at screening, day 14 and end of treatment.

[5]Blood draws: serum and peripheral blood mononuclear cells for later immunological analysis.

[6]Immunology tests: COVID-19 relevant immunology labs (see Appendix 12.1 for complete list). See footnote to Appendix 12.1 as certain labs will be sent to and resulted from outside lab facilities.

[7]Quantitative blood SARS-CoV-2 antibody testing: Blood samples will be used; any FDA-approved or commercial testing method will be acceptable.

[8]WHO 9-point scale: see description of secondary end points for details.

[9]Day 1 (i.e., the first day of drug intake) is most likely also the screen / enroll day; subjects will receive a phone call from Study Team a few hours after first dose is taken to check up on how they are doing.

[10]ET: Subjects who prematurely discontinue study drug for any reason are asked to have an Early Termination (ET) visit the day the last study drug dose was taken.

[11] Subjects will be given a digital thermometer and portable pulse oximeter to record their temperature and oxygenation daily in the provided subject diary.

[12] These laboratory tests will be collected at a one-time blood draw at each visit, a total of 5 collections at the 5 visits (Screening, Day 7, Day 14, Day 21, and Day 28). The amount drawn at each timepoint is as follows: Screening visit (56 mL or 11 teaspoons), Day 7 (44 mL or 9 teaspoons), Day 14 (56 mL or 11 teaspoons), Day 21 (20 mL or 4 teaspoons), and Day 28 (48 mL or 10 teaspoons). The early termination visit would be in lieu of one of the in-person visits, it is not included in the total. Laboratory tests collected at the screening/enrollment visit may be collected by a home health agency in the subjects' home.

[13]Chest x-ray or CT of the chest will be completed as standard of care but not required for screening or randomization or enrollment

## 5.3 Selection Criteria

### Inclusion Criteria:

- Subject (or legally authorized representative) provides written informed consent prior to the initiation of any study procedures.
- Subject understands and agrees to comply with planned study procedures, including using the diary.
- Subject agrees to the collection of nasopharyngeal swabs and venous blood per protocol.
- Subject is male or non-pregnant female adult ≥18 years of age at time of consent.
    - Women with a history of menstruation must agree to use two methods of contraception, at least one of which is highly effective, for the duration of the study as well as to undergo additional pregnancy testing during the study.
- Subject has a laboratory confirmed SARS-CoV-2 infection as determined by RT-PCR assay prior to enrollment.
- Subject has evidence of either mild or moderate COVID-19 illness of less than 7 days from first onset, with minimal baseline symptom severity based on patient-reported FDA scoring system defined as follows:
    - Subject presents with **at least two** common symptoms of COVID-19 from the following list: stuffy or runny nose, sore throat, cough, low energy or tiredness, muscle or body ache,

headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, shortness of breath with exertion (without supplemental oxygen requirement) with a score of 2 or higher; impairment in sense of smell or taste with a score of 1 or higher **OR**

- Subject presents with **any** (i.e., at least one) symptom of COVID-19 as defined above **AND** clinical evidence of moderate COVID-19 as defined by FDA guidance for industry (such as respiratory rate >20 breaths per minute, heart rate >90 beats per minute, with oxygen saturation >93% on room air at sea level).

- Subject presents with high-risk for COVID-19-related inflammation determined by at least one comorbidity, including obesity, diabetes, hypertension, stable heart disease, respiratory disease, and / or non-severe fatty liver disease.
- Subject's overall health condition is deemed as suitable to fully and safely participate in this trial as determined by the Investigator.

**Exclusion Criteria:**

- Any clinical signs indicative of severe or critical COVID-19 as defined by FDA guidance for Industry at the time, including SpO2 < 93% *and / or* oxygen requirement.
- Hospitalization for COVID-19, or consideration thereof.
- ICU level of care and / or non-mechanical / mechanical ventilation *and / or* oxygen supplementation at time of enrollment.
- Pregnant or breast-feeding subjects.
- Subjects who cannot swallow tablets.
- History of any pre-existing organ impairment, such as:
  - Severe kidney disease (known or estimated GFR <30 mL / minute) or on dialysis.
  - Uncontrolled, clinically significant heart diseases such as arrhythmias, angina or heart failure as defined by AHA / ACC Grade C and D.
  - Chronic respiratory disease requiring supplemental oxygen.
  - Moderate and severe hepatic impairment as defined by Child-Pugh scoring Class B and Class C
- Elevated liver function tests (determined by ALT, AST, GGT, or ALP >2 x upper limit of normal, and/or total Bilirubin > upper limit of normal).

- History of malignancy or immunodeficiency within the prior 5 years.
- Acute respiratory illness other than COVID-19.
- Active bacterial, viral or fungal infection (including HIV, hepatitis B, hepatitis C).
- While dosed with the IP, the taking of prohibited concomitant medication or the ingestion of food that interferes with the IP, including:
    - Non-COVID19-related anti-viral medication such as lopinavir, ritonavir, ribavirin or interferon-1β.
    - Systemically administered immunosuppressive and anti-inflammatory agents, other than background standard of care for COVID-19 at the time.
    - Drugs and foods that are potent inhibitors or inducers of CYP3A4 and / or P-gp, as listed in FDA "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers", including herbal medications such as St. John's Wort within 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug.
- Any other diseases or medical conditions or concomitant medications that are deemed as not compatible or appropriate for the subject's ability to fully and safely participate in this trial as determined by the Investigator.

**Discontinuation Criteria and Early Termination Procedures**

Subjects may withdraw voluntarily from participation in the study at any time and for any reason. Subjects may also be withdrawn on the basis of the Investigator's clinical judgment. This study may be terminated at the discretion of MedStar Health or of any regulatory agency for reasons including safety and/or treatment effect.

For enrolled subjects we anticipate that the main reasons for discontinuation of therapy will be either withdrawal of consent for continuation in the study or inability to tolerate the study. Other instances may include patient death, inability to take the study drug from severity of illness or in-hospital complexity of illness. Subjective intolerance of the drug from minor side effects or alternatively cessation of COVID-19 related symptoms well ahead of the 28-day schedule may cause patients to want to discontinue the drug. With regards to drug toxicity itself, we anticipate minor symptomatology from adverse effects, such as headache, dizziness, nausea and vomiting, abdominal discomfort and rash (see also 1.4) based on prior human trial experience with the study drug. Should any subject dosed on the study drug experience seizures, which was reported as an

unrelated adverse event in an epilepsy trial, that individual would be subject to discontinuation out of an abundance of caution. Any emergent symptom that has no clear cause will result in a hold on subsequent study drug dosing until protocol assessment by the Study Investigator. The reasons for discontinuation of study drug will be documented clearly. In all cases study protocol monitoring will continue for the entire 60 days of the protocol as long as the subject stays consented.

When a subject withdraws or is withdrawn before completing the study, the date and reason for withdrawal are to be documented. Subjects who withdraw or who are withdrawn prematurely are to attend an early termination, at which time they will complete all assessments as outlined in the Schedule of Events (Table 1); moreover they will be encouraged to stay enrolled so that further safety and outcome information can be collected and analyzed.

In the event that a subject is withdrawn prematurely due to an adverse event or serious adverse event, the adverse event or serious adverse event will be followed until it resolves or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

### 5.4 Concomitant and Prohibited Medication

At time of enrollment, and at any point during the study, medication or the ingestion of food that interferes with the IP would preclude participation in the study, including:

- Non-COVID19-related anti-viral medication such as lopinavir, ritonavir, ribavirin or interferon-1β.
- Systemically administered immunosuppressive and anti-inflammatory agents, other than background standard of care for COVID-19 at the time.
- In vitro studies suggest that CYP-mediated metabolism is not a major route of clearance for belnacasan (VX-765/RVT-201/MSR-001) or VRT-043198. However, belnacasan (VX-765/RVT-201/MSR-001) was metabolized by CYP3A4 in a recombinant enzyme system.
- Drugs and foods that are potent inhibitors or inducers of CYP3A4 and / or P-gp, as listed in FDA “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers”, including herbal medications such as St. John’s Wort within 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug
- Subjects should also be advised against the consumption of grapefruit juice since it is a known inhibitor of CYP3A.

# 6 MATERIALS

## 6.1 Study Drugs

All study medication will be managed by the MedStar Health Research Pharmacy (RP). The Pharmacy will store and dispense medication to subjects.

For all enrolled subjects, the first dose of study drug will be given orally only after the participant has documented consent, has completed screening and been verified to meet enrollment criteria. This screening visit may occur over more than one day if confirmatory PCR testing is needed. Subjects will be closely monitored for at least 30 minutes to assure they do not experience any untoward effect.

For outpatient subjects (and discharged former inpatient subjects), subjects will be instructed to take subsequent doses at 0600, 1400, 2200 (+/- 4 hours). They will self-record administration in a subject diary (see Appendix) to be reviewed by the study team who will assess compliance at each visit. The study team, under direction of the Investigator, will provide any needed medication education, including adequate storage requirements, with the subject and any relevant family member(s) or caretaker.

For subjects who become inpatients over the course of the trial, study medication will be supplied to the unit in which subjects are admitted and will be dosed by clinical nursing, recorded in the electronic medical record, and overseen by the study team. Doses will be given at 0600, 1400, 2200 (+/- 4 hours). Those who cannot swallow tablets will receive crushed tablets suspended in water and immediately administered through a nasogastric tube, by hospital nursing staff. At discharge and subsequent outpatient visits, enough medication will be dispensed to the subject to assure they have adequate supply until their next on-site follow-up visit.

## 6.2 Storage, Dispensing and Reconciliation of Study Drug and Identity of Investigational Products

All study medication will be stored at room temperature until dispensed. Storage within the RP is locked and secure, accessible only to investigational pharmacy staff. Storage condition temperatures are recorded 24 hours a day, 7 days a week, and 365 days per year and the RP is immediately made aware of any temperature excursions. In such an event, study medication will not be utilized until MedStar Health provides further direction. It is the Investigator's responsibility to ensure that accurate records of study medication dispensation and administration

are maintained. The RP will support the Investigator in medication accountability and dispensation tracking, they have a clear process for return and destruction of investigational medications.

**Table 2: Identification of Investigation Product**

| | |
|---|---|
| **Product Name** | Belnacasan (VX-765/RVT-201/MSR-001) |
| **Dosage form** | Tablet containing 300mg of API |
| **Route/dosage** | Oral |
| **Dosing Instructions** | Three tablets, three times per day (0600, 1400, 2200 +/- 4 hours) |

| | |
|---|---|
| **Product Name** | Placebo |
| **Dosage form** | Tablet containing 0mg of API |
| **Route/dosage** | Oral |
| **Dosing Instructions** | Three tablets, three times per day (0600, 1400, 2200 +/- 4 hours) |

# 7 STUDY PROCEDURES

## 7.1 Observations and Measurements

Subject informed consent must be obtained prior to conducting any study-specific procedures. The informed consent can be signed by the subjects' legally authorized representative (LAR) if necessary. The Investigator will assure that each subject/LAR is adequately consented to the requirements of participation including the potential risks and benefits and voluntary nature of the trial that he or she is free to discontinue participating in the study at any time. The subject/LAR will be given the opportunity to ask questions and allowed adequate time to consider the information provided. All assessments and procedures will be completed according to the Schedule of Events. A custom subject diary has been developed for this study. The diary will be tested for basic comprehensibility before finalizing and using with subjects. The study teams may consent subjects by remote consent process that may include the use of an e-consent platform, Interlace, for documentation of consent if they are no longer at a MedStar site. In this circumstance initial contact will be made with potential subjects via telephone to discuss the trial followed by any subsequent discussions needed to assure consent is obtained per Institutional policy and procedure, as approved by the IRB. The study team will communicate with the home health agency directly to schedule the collection of the RT-PCR and screening labs, once consent is obtained, for a time that is convenient to the subject. Following collection, the agency will transport these tests to MedStar Georgetown University Hospital for resulting. Once eligibility is confirmed by PCR the

subject will return to either MedStar Washington Hospital Center or MedStar Franklin Square to complete the remainder of the screening/enrollment visit.

### 7.2 Instructions to Subjects

At enrollment, the Study Team will explain the subject diary (see Appendix) and ensure they understand what to enter in each field. They will be told about the importance of collecting the information in the diary for scientific purposes, and that even if they discontinue intake of the study drug, they should continue to participate in the study, continue to fill in the diary, and continue to attend planned study visits.

For outpatient subjects (and discharged former inpatient subjects), subjects will be instructed to take 3 tablets of IP at 0600, 1400, 2200 (+/- 4 hours) for up to 28 days. They will self-record administration of the IP in the subject diary to be reviewed by the study team who will assess compliance at each visit. The study team, under direction of the Investigator, will provide any needed medication education, including adequate storage requirements, with the subject and any relevant family member(s) or caretaker.

For subjects who become inpatients over the course of the trial, study medication will be supplied to the unit in which subjects are admitted and will be dosed by clinical nursing, recorded in the electronic medical record, and overseen by the study team. Doses will be given at 0600, 1400, 2200 (+/- 4 hours). Those who cannot swallow tablets will receive crushed tablets suspended in water and immediately administered through a nasogastric tube, by hospital nursing staff. As study medication will be administered by hospital staff, and there are no specific instructions to subjects. At discharge and subsequent outpatient visits, enough medication will be dispensed to the subject to assure they have adequate supply until their next on-site follow-up visit.

Women with a history of menstruation must agree to use effective method of contraception and protections that align with International Council on Harmonization M3 R2 guidelines for highly effective methods of contraception for the duration of the study (i.e., two forms of contraception, whereby one result in a less than 1 percent per year failure rate when used consistently and correctly), as well as to undergo additional pregnancy testing during the study on day 14. Details of all pregnancies in female participants will be collected for 60 days after randomization.

**Warnings and Precautions**

Subjects will be watched carefully for signs of previously documented symptoms in human patients that have received belnacasan (VX-765/RVT-201/MSR-001), as well as symptoms to indicate a drug reaction or new symptoms that could be temporally attributable to the drug. The most frequent adverse effects in humans have been mild and mainly include headache, nausea, lethargy and dizziness. No serious side effects have been described in human and animal studies.

### 7.3 NCI CTCAE Definitions of Dose Limiting Adverse Events

The National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE) will be used for monitoring adverse events throughout study including those related to dose limitation. As noted above in section 7.2, adverse events with belnacasan (VX-765/RVT-201/MSR-001) have been mild and of no consequence (grade 1 and 2 by CTCAE criteria, see below section 7.8). There is no dose escalation in this trial that could result in new symptoms though it is possible that mild symptoms may become more severe.

### 7.4 Pre-Existing Medical Conditions

All subjects enrolled in the study will have SARS-CoV-2 infection and at least two moderate COVID-19 symptoms or one moderate symptom and clinical evidence of moderate COVID-19. Subjects will present with high-risk for COVID-19-related inflammation, due to at least one comorbidity, including obesity, diabetes, hypertension, stable heart disease, respiratory disease, and / or non-severe fatty liver disease.

### 7.5 Acute Conditions Brought on by COVID-19

The development of acute kidney and/or hepatic injury has been reported as a possible complication during the disease progression of COVID-19. Acute kidney and/or hepatic injury will be addressed in the following manner depending on whether at, (1) enrollment, (2) during the study period when drug is being administered in an ambulatory setting, (3) or during admission to hospital for COVID-19 related deterioration or other illness.

1. Potential participants in this study will undergo initial screening evaluation at a MedStar site or via a home health visit which includes background laboratory testing. If the testing indicates renal failure, GFR <30 or features of acute renal failure, most notably anuria, edema on examination in a previously healthy individual, the potential participant will not be enrolled as per the inclusion criteria or otherwise clarified with the nephrology consultant managing the patient. Similarly, potential participants shown to have evidence

of elevated liver function tests (determined by ALT, AST, GGT, or ALP >2 x upper limit of normal, and/or total Bilirubin > upper limit of normal) will not be enrolled in the study.

2. Laboratory testing throughout the study period (see Section 5.2 Table 1) may, though unlikely, show an acute change in renal or liver testing to indicate acute organ-specific disease or involvement as a possible complication of COVID-19. In such a circumstance, subjects will be directed to seek care from the respective hospital/specialist. In the case of acute liver injury with functional impairment, the IP will be discontinued immediately after blood has been taken for future assessment of drug levels. In the case of subjects with elevated liver function tests suggestive of acute liver injury without functional impairment, IP will be held to discern in the first instance the possibility of an adverse event and restarted in consultation with the managing hepatologist if it is determined to be COVID-19 related hepatopathy. In the case of subjects with acute renal injury, IP will be held to discern in the first instance the possibility of an adverse event and restarted in consultation with the managing nephrologist if it is determined to be COVID-19 related nephropathy. DSMB guidelines for unblinding will be followed in these cases as relevant.
3. Acute liver and kidney injury may be seen in the face of hospital admission in patients with worsening COVID-19, in which case the patients will be managed similarly to number 2 above (also see Section 5.3 on discontinuation).

### 7.6 Treatment Emergent Adverse events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following the start of IP administration.

Adverse events will be captured following the first dose of IP and could be related or unrelated to the study drug. A TEAE is defined as any AE that occurs after the subject takes the first dose of IP.

Separate summaries for adverse events that occur during treatment (summary of treatment emergent adverse events) will be provided.

### 7.7 Laboratory Abnormalities

Clinical labs will be performed locally at WHC or other MedStar clinical sites. Labs to be drawn during the study include serum chemistries, a hematology panel and an immune panel (see Appendix 12.1 for more details). A serum pregnancy test must be performed, and the result must be negative prior to the entry of women of child-bearing potential.

Clinical laboratory reports must be reviewed by a physician for out-of-range values within 12 hours of receipt. Out-of-range values will be evaluated using the following notations:

- NCS: Not clinically significant
- LE: Laboratory Error
- PT: Subject abnormal; relates to the subject's usual state of health
- CS: Clinically Significant. This value cannot be explained by any of the other indicators.

By definition a lab value flagged as "CS" indicates an adverse event and will be captured on the CRF. A laboratory test flagged "CS" should be repeated as soon as possible, then the Investigator should use his or her judgment as to whether the abnormal finding is sufficient reason to immediately withdraw the subject from the study.

If a laboratory value is considered to be serious and life-threatening and at least possibly related to the study drug, the subject should be immediately discontinued from the study and appropriate therapy started. Refer to Sections 7.8 to Section 7.13 for definition of a serious adverse event and related terms, and details on reporting a serious adverse event.

Particular attention will be paid to determine the possibility of drug induced liver injury (DILI) as detailed in the FDA guidance document “Drug-Induced Liver Injury: Premarketing Clinical Evaluation.” Liver tests (ALT, AST, ALP, and total Bilirubin) will be performed at enrollment and at days 7, 14, and 28 throughout the drug administration period. For patients exhibiting signs of liver disease such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash, extensive laboratory testing will be performed that includes above liver chemistries immediately. Otherwise, on routine weekly testing an increase of serum aminotransferase levels to >3x upper limit of normal would automatically trigger repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and total Bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. If symptoms and/or aminotransferase levels remain >3x upper limit of normal, the participant will be monitored more

closely with lab schedule, in-person or virtual evaluation twice weekly or more. A thorough evaluation for additional causes of liver test anomalies will be conducted in consultation with Hepatology. A case report form page will be created and DSMB review triggered. Otherwise, discontinuation of treatment will be considered immediately if:

- ALT or AST >8x upper limit of normal
- ALT or AST >5x upper limit of normal for more than 2 weeks
- ALT or AST >3x upper limit of normal and total Bilirubin >2x upper limit of normal or INR >1.5
- ALT or AST >3x upper limit of normal with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

### 7.8 Adverse Event Assessment and Recording

All adverse events, exacerbations of concomitant illnesses, or events known to be related to underlying disease processes or concomitant medications are to be recorded on the CRF throughout the study. If a pre-existing condition worsens during the study, the date on which the exacerbation began should be recorded. Onset dates for study treatment-related adverse events must be on or after the date of initial study treatment use.

Adverse event recording will include the date of onset, severity, duration, whether or not the study medication was discontinued because of the event, the treatment given, and the outcome. The Investigator must also assess whether the event was related to the study medication, concurrent drug therapy, underlying disease, a combination of these factors, or if it is unknown. Subjects experiencing an adverse event should be carefully followed to determine outcome.

The Investigator will use the NCI-CTCAE for adverse event monitoring, version 5.0 will be applied in all instances. CTCAE version 4.03 may also be used especially when assessing laboratory tests given the complexity in applying version 5.0 in all instances, see www.lexjansen.com/phuse-us/2020/dh/DH16.pdf

**Definitions to grade the severity of the event:**

**Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

**Grade 2:** Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate ADL.

**Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

**Grade 4:** Life-threatening consequences; urgent intervention indicated.

**Grade 5:** Death.

The relationship or association of the study medication in causing or contributing to the adverse event will be characterized as not related, remote, possible, probable, or definite as defined below:

- **Not related:** Evidence indicates no plausible direct relationship to the study medication
- **Remote:** Suggests other conditions are reasonably likely to account for the event including concurrent illness, progression or expression of the disease state, or reaction to concurrent medication
- **Possible:** Suggests that the association of the event with the study medication is unknown; however, the adverse event is not reasonably supported by other conditions
- **Probable:** Suggests that a reasonable temporal sequence of the event with medication administration exists and based upon the Investigator's clinical experience, the association of the event with study medication seems likely
- **Definite:** Suggests that based upon the Investigator's experience, the association of the event with the study medication seems very certain.

Planned procedures such as surgery should not be recorded as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of adverse event.

### 7.9 Reporting Requirements

Any adverse event, defined below, that begins any time between the start of the first dose and within 28 days after the end of the last dose are to be recorded on the appropriate CRF and in detail in the source documentation (preferably the electronic medical record directly).

**Adverse Event:** Any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An adverse event can be any unfavorable sign (including an abnormal laboratory finding), symptom,

or disease temporally associated with the use of the investigational drug, whether or not considered related to the investigational drug.

**Serious Adverse Event:** An untoward event or reaction that at any dose:

- results in death
- is life-threatening
- results in hospitalization or prolongs existing hospitalization
- results in permanent or significant disability or incapacity
- requires intervention to prevent permanent impairment/damage
- results in congenital anomaly or birth defect

In addition, any important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**Life-threatening:** An event which a subject was at risk of death at the time of event. There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity, thus a severe reaction is not necessarily a serious adverse event. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events listed previously.

### 7.10 Serious Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) will be collected from the time the first dose of IP is administered until 28 days after the last dose of IP. Medical occurrences that began prior to the start of study treatment, but after obtaining informed consent will be captured as Medical History/Current Medical Conditions on the CRF. The Investigator or site staff will be responsible for the identification and documentation of events meeting the criteria and definition of an adverse event or serious adverse event, as provided in the study protocol. SAEs assessed as related to study participation (e.g., dosing, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication will also be captured once the subject has taken the first dose of study medication.

In the event of an AE or SAE, it will be the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event and attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. Once the Investigator becomes aware that an SAE has occurred, they are to report the information to MedStar Health within 24 hours and provide an assessment of causality.

### 7.11 Notification of Serious Adverse Events

The Sponsor will report all serious adverse events to regulatory agencies as required. In addition to the serious adverse events described in Section 7.10, other events that in the Investigator's opinion suggest a significant hazard, contraindication, or precaution should be considered serious. This includes, but is not limited to, blood dyscrasias, endocrine disturbances, hemorrhage from any site, or severe skin disorder. Additional examples are intensive treatment for allergic bronchospasm, blood dyscrasias or convulsions.

Subjects who experience an SAE must be given appropriate examinations and treatment. The Investigator must provide written information to the Sponsor as soon as possible.

### 7.12 Reporting a Serious Adverse Event

All appropriate SAEs will be reported immediately to the FDA per reporting criteria for an IND Safety Report. The event(s) will also be reported locally to the IRB of record when the event meeting reporting criteria per MedStar Health Research Institute IRB policy.

### 7.13 Departure from Protocol for Emergency or Adverse Event

In medical emergencies, the Investigator should use medical judgment and remove the subject from immediate hazard. As soon as possible after removing the subject from hazard, the Investigator must contact MedStar Health by telephone to permit a decision as to whether the subject may continue in the study. The IRB should also be notified as to the type of emergency and the course of action. The CRF for the subject must capture the departure from the protocol and state the reason.

### 7.14 Safety Monitoring

A Data Safety and Monitoring Board (DSMB) will be established to monitor the safety of the subjects during the study. The DSMB includes members who are independent of this study and its Sponsor Team, and with relevant clinical expertise, including a good understanding of the safety

of medications for respiratory illnesses. These members may include one or more of the following- a statistician, an infectious disease specialist and/or a pulmonologist. The methodology and the operating procedures for the safety reviews will be developed by the infectious disease specialist and/or pulmonologist in collaboration with the Investigator and will be documented in the DSMB Charter. They will review all SAEs and determine whether the study can proceed or whether protocol modifications are required. The Charter will be submitted to the IND before the trial would commence.

### 7.15 Stopping Rules

Should two or more subjects develop a similar Grade 3 SAE that is at least possibly related to belnacasan or should one or more subjects develop a ≥ Grade 4 SAE that is at least possibly related to belnacasan, the trial will be paused for DSMB safety review.

### 7.16 Follow-Up and Final Reports

The Investigator shall provide MedStar Health with an accurate final report within 1 month after completion, termination or discontinuation of the study. The final report may not precede completion of monitoring relevant CRFs.

### 7.17 Regulatory Aspects

Neither the Investigator nor MedStar Health shall modify this protocol without first obtaining concurrence of the other in writing. All modifications must be submitted to the IRB with approval prior to implementation. Protocol modifications which impact subject safety or the validity of the study must be approved by the IRB and submitted to the FDA before implementation. In the case of a medical emergency to increase safety of subjects, a change may occur immediately, and the IRB and FDA will be notified as soon as possible.

## 8 DATA MANAGEMENT AND STATISTICS

### 8.1 Populations for Analyses

The following populations will be considered for statistical analyses.

- ***Safety & Tolerability Population***: All enrolled subjects who have received at least 1 dose of IP (belnacasan or placebo) will be studied. Even if subjects have discontinued study treatment, as long as they maintain consent, they will continue to be in the study and

included in analysis, i.e., their safety and tolerability information will continue to be collected for at least 60 days.

- ***Treatment Effect Evaluable Populations***: All enrolled subjects who have received at least 1 dose of IP (belnacasan or placebo) will be studied. Even if subjects have discontinued study treatment, as long as they maintain consent, they will continue to be in the study and included in analysis, i.e., their outcome information will continue to be collected for at least 60 days.

## 8.2 Analysis Methods

### General Methods

FDA Data Standard Guidelines will be followed. Continuous variables will be summarized using the number of observations, number of observations above the limit of quantification (if applicable), mean, standard deviation (SD) median, and range. Categorical variables will be summarized using frequency counts and percentages. Comparison of belnacasan (VX-765/RVT-201/MSR-001) and placebo groups will utilize Poisson regression for counts, Cox proportional hazards regression for time-to-event data and mixed effects models for continuous and categorical data obtained over study days.

## 8.3 Analysis of Subject Disposition, History, and Baseline Characteristics

Subject disposition, including analysis population allocation, subjects enrolled, completed each period, discontinued, and primary reason for discontinuation, will be summarized using frequency and percentage. Protocol deviations will be summarized using frequency and percentage. Medical history data and prior and concomitant medications will be summarized using frequency and percentage. Subjects' age, height, weight, and baseline disease characteristics will be summarized using descriptive statistics. Gender, race, and other categorical variables will be provided using frequency and percentage.

## 8.4 Safety & Tolerability Analyses

All safety & tolerability analyses will be performed on the Safety Population. The safety data will be presented in individual listings and summary tables.

Overall safety will be assessed by the number of belnacasan VX-765/RVT-201/MSR-001 dosed subjects experiencing a grade 4 or 5 SAE during the trial. Of 20 subjects enrolled in the belnacasan group, 3 or more developing a grade 4 or 5 SAE probably related to belnacasan would be

considered unlikely due to chance. Therefore, belnacasan will be determined safe if no more than 2 subjects develop a grade 4 or 5 SAE in the belnacasan group probably related to belnacasan.

In terms of stopping rules, should two or more subjects develop a similar Grade 3 SAE that is at least possibly related to belnacasan or should one or more subjects develop a ≥ Grade 4 SAE that is at least possibly related to belnacasan, the trial will be paused for DSMB safety review.

**Primary Endpoint Analysis**

Primary endpoints of adverse and serious adverse events (AE/SAE) will be assessed by Poisson regression for count data. Events will be counted out to 60 days from randomization to belnacasan or placebo groups. Because some subjects may be followed for less than 60 days, subject follow-up time will be included in the Poisson regression as the exposure time variable. If counts are not Poisson-distributed, either over- or under-dispersed, negative binomial regression will be to analyze AE/SAE events with appropriate adjustment for over/under dispersion. Comparison of belnacasan vs. placebo will be expressed as the incidence rate ratio (IRR).

**Adverse Events**

AEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The intensity/severity of AEs will be graded according to NCI-CTCAE (see Section 7.3).

TEAEs, AEs leading to study treatment discontinuation, AEs leading to dose interruption, AEs related to study medication, SAEs, and AEs leading to death will be summarized by system organ class, preferred term, and study period. A summary of AEs that are CTCAE Grade 3 or higher, as well as the most frequent preferred terms, will be provided.

If a subject experiences the same adverse events multiple times within a period, then the event will be counted only once within the period and by greatest severity.

Descriptive statistics will be used to summarize the safety data.

**Clinical Laboratory Values**

All laboratory test results will be summarized by period together with the change from baseline. The frequency distribution for low/normal/high or normal/abnormal will be summarized as well.

The denominators for calculating the percentages will be based on the number of subjects with non-missing values in the Safety Population.

**Vital Signs**

Vital sign results will be summarized by period, together with the change from baseline.

**Physical Examination**

Summaries of physical examinations will present frequency distribution of abnormal findings by body system and period. The denominators for calculating the percentages will be based on the number of subjects evaluated for a particular body system of each dose level in the Safety Population.

**Electrocardiogram (EKG)**

EKG findings will be classified as normal vs abnormal. The number and percentage of each category will be summarized using frequency table for each period. The denominators for calculating the percentages will be based on the number of subjects with non-missing values in each period.

### 8.5 Treatment Effect Analyses

**Secondary Endpoint Analyses**

**Event counts** over 60 days will be analyzed by Poisson regression as described above in 8.4. **Time to events** will be analyzed by Cox regression. Differences between belnacasan and placebo with respect to change in continuous endpoints will be assessed by mixed effects models for **continuous repeated measures data** and mixed effects logistic models for **repeated categorical variables**. Endpoint proportions of belnacasan and placebo groups will be assessed by **contingency table analysis** (chi-square).

### 8.6 Handling of Missing Data

Although every effort will be made to obtain complete data, missing values will likely occur when data are collected longitudinally. Patterns of missingness over time as well missingness with

respect to demographic and clinical variables will be assessed. For Poisson and Cox regression analyses, all data can be used up to subject dropout time.

### 8.7 Sample Size Considerations

A total of 40 subjects will be randomized, 20 to belnacasan (VX-765/RVT-201/MSR-001) 900 mg TID and 20 to placebo. As this is a proof-of-concept study, it will likely not be powered to detect belnacasan – placebo differences that are clinically meaningful. For example, the observed difference in endpoint rate ratios would need to be over 60% to achieve 80% power with an alpha error rate of 5% for 20 subjects in each group. This study will provide an estimate of the belnacasan effect size to inform a larger trial where a more clinically meaningful difference can be detected.

## 9 ESTIMATED DURATION OF THE STUDY

This study has an estimated maximum duration of up to 8.5 weeks for each subject. The study duration from first subject enrolled to last subject enrolled is expected to be 3-6 months.

## 10 ADMINISTRATIVE PROCEDURES AND ETHICAL CONSIDERATIONS

### 10.1 Subject Information and Informed Consent

The Investigator will ensure that the subject/LAR fully understands study participation requirements including possible risks and benefits. Subjects must also be notified that they are free to withdraw from the study at any time. During the informed consent process, the subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subjects' informed consent must be obtained before conducting any study-specific procedures.

### 10.2 In person consent

When participants are recruited from one of the primary MedStar research sites and consented while on site a standard consent process will be used in accordance with institutional policy and procedures. (MG.O-004.01)

### 10.3 Remote Consent

Remote consent may be used for participants that are identified as potentially eligible for the study but are no longer present at one of the primary MedStar Research sites or received treatment at another MedStar Emergency Department or Urgent Care facility. In all cases remote consent will be conduced in accordance with MedStar policies and procedures (MG.O-004.06).

## 10.4 Documentation of Consent

In all cases consent will be documented before research procedures begin. Standard documentation of consent may be used including presentation of a paper consent for to a potential participant for signature. This form of documentation of consent may be used for either with an in person or remote consent process. In all cases documentation of consent will be obtained in accordance with institutional policy and procedures (MG.O-004.01, MG.O-004.06).

**Electronic Consent**

Electronic consent (eConsent) may be used for documentation of consent for both participants that are consented in person and those that are consented via a remote process. In all cases eConsent will be conducted in accordance with institutional policies and procedures (MG.O-004.07).

## 10.5 Study Monitoring

During the study, a dedicated Clinical Research Associate (CRA) will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator,
- Confirm that facilities remain acceptable,
- Confirm that the investigational team is adhering to the protocol, that data is being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed,
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subjects' medical records, and other records relevant to the study. This will require access to all original records for each subject (e.g., clinic charts) as described in the study monitoring plan.
- Record and report any protocol deviations not previously sent to MedStar Health.
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to MedStar Health, and those serious adverse events that met criteria for reporting have been reported to the IRB.

The CRA will be available over the course of the study if the Investigator or other staff needs information or advice. Remote visits will be conducted until it is possible to perform on-site visits.

### 10.6 Audits and Inspections

Authorized representatives of the FDA, or the Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of any inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and FDA regulations. The Investigator / Sponsor should contact the site immediately if contacted by a regulatory agency about an inspection.

### 10.7 Ethics Committee Review

The final study protocol, including the final version of the Informed Consent Form, must be approved by the MedStar Health Research Institute IRB.

The Sponsor is responsible for submitting any modifications to the Protocol to the IRB and obtaining approval in advance of implementing these modifications. In addition, the IRB must approve all advertising used to recruit subjects for the study. The study must also be renewed annually with the IRB as long as study conduct is occurring.

The Investigator / Sponsor are also responsible for providing the IRB with reports of any reportable new information (RNI) including any serious adverse drug reactions from any other study conducted with the investigational product.

### 10.8 Standards

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

### 10.9 Confidentiality

Any research information obtained specific to subjects enrolled into this study will be kept confidential. A subject will not be identified by name, only by a unique study number. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subjects' participation in the study may be disclosed with his/her consent to the healthcare providers for the purpose of obtaining appropriate

medical care. The subject's medical records/charts, tests with his/her name on them may be made available to the appropriate contract research organization (CRO), MedStar Health, IRB, and the FDA. This is for the purpose of verifying information obtained for this study.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the Investigator and will not be transferred outside of WHC / MedStar as applicable.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the data about the subject that has already been collected may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

### 10.10 Protocol Adherence

The records of study treatment delivered to subjects and IP inventory will be maintained at WHC / MedStar; the administration to each subject; and storage or disposal of any unused IP. These records should include dates, quantities, batch/serial numbers, expiration dates, IDS temperature log, and unique code numbers assigned to the product and study subjects.

The Investigator will maintain records that document adequately that the subjects were provided with the correct study drug and will maintain IP accountability and tracking records.

### 10.11 Amendments to the Protocol

Modifications to the protocol are only possible by approved protocol amendments authorized by the Sponsor, approved by the IRB, and deemed as not-objectionable by the FDA. The Investigator must not implement any deviations from, or changes to the protocol, except where it is necessary to eliminate an immediate hazard to the study subject.

### 10.12 Protocol Deviations

The protocol must be conducted compliantly, significant deviations from the protocol will be reported to the FDA and/or IRB per policy.

### 10.13 Study Termination

This study may be prematurely terminated, if in the opinion of the Investigator or MedStar Health there is sufficient reasonable cause. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Failure to enroll subjects at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend, or discontinue the development of belnacasan (VX-765/RVT-201/MST-001).

### 10.14 Inspection of Records

MedStar Health will be allowed to audit data for the purpose of monitoring any aspect of the study they deem necessary, pursuant to local restrictions on monitoring due to health concerns. The Investigator agrees to allow the IRB and regulatory authorities to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. Remote access can be granted in the event the pandemic prevents on-site monitoring.

### 10.15 Data Management

All data relating to study procedures will be entered onto the eCRF (OnCore platform). CRF completion guidelines will be developed to assure the required data is appropriately captured. eCRFs will be completed for each subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data entered in each subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and document the dates and details of study procedures, adverse events, and subject status.

The Investigator, or designee, should complete the eCRF as soon as possible after data is collected, preferably on the same day that a subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be entered immediately after the final examination. An explanation should be given for all late or missing data.

### 10.16 Liability and Insurance

*Subject Injury*: Sponsor will not provide reimbursement if any subject suffers an adverse reaction, illness, or injury, which is determined to have been caused directly by the subject's participation in the study.

*Insurance*: Sponsor shall, at its sole cost and expense, maintain a policy or program of insurance or self-insurance in compliance with applicable law in amounts sufficient to cover Sponsor's liabilities and obligations in connection with the study.

### 10.17 Retention of Records

Investigators shall retain study records and source documents for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified and / or the period required by local, state, and federal laws, regulations and FDA Guidance.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of protected health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation.

### 10.18 Data Quality Assurance

WHC / MedStar and all relevant subject study and medical records may be subject to a quality assurance audit during the course of the study. In addition, inspections may be conducted by the FDA at their discretion.

If sites receive a request for an inspection or written or oral inquiries regarding any aspect of institution's or Investigator's activities related to this study from a regulatory authority, the Investigator must immediately notify MedStar Health of the request. Following this inspection and/or audit, the Investigator must notify MedStar Health of any violation or deficiency noted by the regulatory authority.

## 11 USE OF INFORMATION

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and MedStar Health or their designee. With respect to such rights, MedStar Health or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions directly to MedStar Health or its designee, as will be set forth in the clinical study agreement.

# 12 APPENDIX

## 12.1 Labs and Tests

| Hematology |
|---|
| Complete Blood Count:<br>White Blood Cell (WBC) Count<br>Red Blood Cell (RBC) Count<br>Hemoglobin (Hb)<br>Hematocrit (Hct)<br>Mean Corpuscular Volume (MCV)<br>Red Blood Cell Distribution Width (RDW)<br>Platelet Count |
| Differential - absolute and percent of:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Coagulation Tests:<br>Partial Thromboplastin Time (PTT)<br>Prothrombin Time (PT) |
| Immune Cell Counts – absolute and percent of:<br>CD3+ T cells[1] |
| Serum and Plasma Levels of Cytokines and Inflammasome Markers[2]:<br>IL-18<br>IL-1β<br>IL-1 receptor antagonist<br>IL-6<br>Gasdermin D<br>G-CSF<br>TNF-α<br>Caspase-1 |

| Serum Chemistry |
|---|
| Albumin<br>Alanine Aminotransferase (ALT)<br>Alkaline Phosphatase (ALP)<br>Aspartate Aminotransferase (AST)<br>Blood Urea Nitrogen (BUN)<br>Calcium<br>Carbon Dioxide<br>Chloride<br>Creatinine<br>Glucose<br>Lipase<br>Magnesium<br>Potassium<br>Sodium<br>Total Bilirubin<br>Total Protein<br>Lactate Dehydrogenase (LDH)<br>Creatine Kinase, Total<br>CRP<br>Ferritin<br>D-Dimer<br>HbA1c<br>Troponin I, High Sensitivity (hs-TnI) |

| Screening Tests |
|---|
| HIV |
| Hepatitis B |
| Hepatitis C |
| Pregnancy (serum pregnancy test for women of child-bearing potential per MedStar definition at enrollment and once during IP course) |

[1] CD3+ counts/cell isolation/storage for future research samples will be sent to for resulting/storage:
Cell Therapy Manufacturing Facility
MedStar Georgetown University Hospital
3800 Reservoir Rd NW, Room M1334
Washington, DC 20007

[2] Cytokines and inflammasome markers will be sent/resulted to/from:
University of Maryland Cytokine Core Laboratory
655 West Baltimore Street, Bressler Research Bldg, 7th Floor, Room 07010
Baltimore, MD 21201

## 12.2 Illustrative Subject Diary Excerpts

### Subject Diary – Overview of Study Events

| | Days | | | | | | |
|---|---|---|---|---|---|---|---|
| **Week 1** | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Week 2** | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| **Week 3** | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| **Week 4** | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| **Week 5** | 29 | 30 | 31 | 32 | 33 | 34 | 35 |
| **Week 6** | 36 | 37 | 38 | 39 | 40 | 41 | 42 |
| **Week 7** | 43 | 44 | 45 | 46 | 47 | 48 | 49 |
| **Week 8** | 50 | 51 | 52 | 53 | 54 | 55 | 56 |
| **Week 9** | 57 | 58 | 59 | 60 | | | |

*Legend*

***Days 1-28**:* Three times per day: take the study drug;
Once every morning: rate your symptoms and overall health and record your temperature and oxygen saturation levels

***Days 1, 4, 10, 42, 60**:* Receive phone calls from Study Team

***Days 7, 14, 21, 28**:* Visit Study Center in person

***Days 7, 14, 21, 28**:* Give Study Team last 7 days of Diary pages

# Subject Diary – Sample Daily Log – Page 1

**Date:** _____ **Subject Number:** _____

## Common COVID-19 Symptoms

Time you are filling this out today: _____

What was the **SEVERITY** of these symptoms <u>at their worst</u> in the last 24 hours? Place an **X**

| | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| **Stuffy or runny nose** | | | | |
| **Sore throat** | | | | |
| **Shortness of breath at rest** | | | | |
| **Shortness of breath with exertion** | | | | |
| **Cough** | | | | |
| **Low energy or tiredness** | | | | |
| **Muscle or body aches** | | | | |
| **Headache** | | | | |
| **Chills or shivering** | | | | |
| **Feeling hot or feverish** | | | | |
| **Nausea** | | | | |

In the last 24 hours, <u>how often</u> did you have these **ISSUES**? Place an **X**

| | 0 times | 1-2 times | 3-4 times | 5 or more times |
|---|---|---|---|---|
| **Vomit** (throw up) | | | | |
| **Diarrhea** (loose or watery stools) | | | | |

In the last 24 hours, how would you <u>rate</u> your **SENSES**? Place an **X**

| | SAME as usual | LESS than usual | I have NO sense |
|---|---|---|---|
| **Sense of smell** | | | |
| **Sense of taste** | | | |

Over the last 24 hours, if there were **any other symptoms** beyond the ones listed above that you experienced, please describe them here:

# Subject Diary – Sample Daily Log – Page 2

**Date:** _____ **Subject Number:** _____

## Global Health Impression

Time you are filling this out today: _____

Place an **X**

| | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| In the past 24 hours, what was the severity of your **OVERALL** COVID-19-related symptoms at their worst? | | | | |

| | Yes | No |
|---|---|---|
| In the past 24 hours, have you returned to your usual **HEALTH** (before your COVID-19 illness)? | | |
| In the past 24 hours, have you returned to your usual **ACTIVITIES** (before your COVID-19 illness)? | | |

## Temperature

Record your temperature from the thermometer and note the time you took the measurement; if your temperature is **higher than 100.4 F**, please call your Study Nurse

| Temperature | Time |
|---|---|
| °F | am |

## Oxygen ($O_2$) Saturation

Record your oxygen saturation from the pulse oximeter and note the time you took the measurement; if your oxygen saturation is **lower than 93%**, please call your Study Nurse

| $O_2$ Saturation | Time |
|---|---|
| %$SpO_2$ | am |

## Medication

Place an **X** to note that you have taken 3 tablets of the **STUDY DRUG** and note the time you took them; remember you will take 9 tablets total each day

| Morning | Mid-Day | Evening |
|---|---|---|
| | | |
| am | _m | pm |

Note any **OTHER** medications, vitamins, or supplements you took, other than those you told us at enrollment that you take on a regular basis; use the back of this page if you need more space

| Name | Dose | Time |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

## 12.3 Illustrative Randomization Table

A randomization table such as the one below will be used to allocate subjects to belnacasan or placebo group (N=20 each). Assignment of A or B to treatment or placebo blinded to subjects and investigators.

| Sequential subject | Group assignment | Sequential subject | Group assignment |
|---|---|---|---|
| 1 | A | 21 | B |
| 2 | B | 22 | A |
| 3 | B | 23 | A |
| 4 | A | 24 | B |
| 5 | A | 25 | A |
| 6 | B | 26 | B |
| 7 | A | 27 | A |
| 8 | B | 28 | B |
| 9 | A | 29 | A |
| 10 | A | 30 | A |
| 11 | B | 31 | B |
| 12 | B | 32 | B |
| 13 | B | 33 | B |
| 14 | A | 34 | B |
| 15 | A | 35 | A |
| 16 | B | 36 | A |
| 17 | B | 37 | B |
| 18 | A | 38 | A |
| 19 | B | 39 | B |
| 20 | A | 40 | A |

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