Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19 to Reduce the Burden of Illness for U.S. Service Members

Patrick Ng, MD
Adit Ginde, MD, MPH
Col Vik Bebarta, MD
Nathan Shapiro, MD, MPH
Todd Rice, MD
Lt Col Joe Maddry, MD

FINAL REPORT

Date: 01/23/2023

59th Medical Wing
Office of the Chief Scientist
1632 Nellis, BLDG. 5406
JBSA Lackland AFB, TX 78236-7517

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DECLARATION OF INTEREST

The views expressed in this are those of the authors and do not reflect the official policy Department of Defense or it's Components. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02. This work was funded by Project Code Number AC20COV08. Authors are military service members, employees, or contractors of the US Government. This work was prepared as part of their official duties. Title 17 USC §105 provides that 'copyright protection under this title is not available for any work of the US Government.' Title 17 USC §101 defines a US Government work as a work prepared by a military service member, employee, or contractor of the US Government as part of that person's official duties.

NOTICE AND SIGNATURE PAGE

RETROSPECTIVE COHORT STUDY OF BURN CASUALTIES TRANSPORTED BY THE US ARMY BURN FLIGHT TEAM (BFT) AND US AIR FORCE CRITICAL CARE AIR TRANSPORT TEAMS (CCATT)

Michele F. Tavish

Michele F. Tavish, DHA
Program Analyst
En route Care Research Program
59MDW Office of the Chief Scientist

Robert T. Gerhardt, MD, MPH, FACEP, DHA
Director, Trauma & Clinical Research
59MDW Office of the Chief Scientist

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
23Jan 2023	Final Report	May 2020 – December 2022

4. TITLE AND SUBTITLE

Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19 to Reduce the Burden of Illness for U.S. Service Members

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Maj Patrick Ng, MD
Col Vik Bebarta, MD
Adit Ginde, MD, MPH
Nathan Shapiro, MD, MPH
Todd Rice, MD
Lt Col Joe Maddry, MD

5d. PROJECT NUMBER
AC20COV08

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

59th Medical Wing, JBSA-Lackland, TX
University of Colorado – Denver | Anschutz Medical Campus as lead for 12 clinical sites i
Vanderbilt University Medical Center as the Data Coordinating Center

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Vanderbilt University Medical Center
1211 Medical Center Drive
Nashville, TN 37232

AbbVie Inc.
1 N. Waukegan Road
North Chicago, Illinois 60064

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
AC20COV08

12. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution A: Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT-

Effective and widely available therapies are still needed for outpatients with COVID-19 to reduce progression to severe disease, improve symptom resolution, and expedite return to duty. We aimed to evaluate the efficacy and safety of the antiviral agent lopinavir/ritonavir for early treatment of non-hospitalized individuals diagnosed with COVID-19. The Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) was an adaptive platform trial to evaluate potential antiviral therapies for the treatment of COVID-19. This randomized, placebo-controlled, double-blind decentralized clinical trial was coordinated by five sites within the United States. Participants were non-hospitalized adults with confirmed SARS-CoV-2 infection and six or fewer days of acute respiratory infection symptoms who were randomized to either twice daily oral lopinavir/ritonavir (400 mg/100 mg) or placebo for 14 days. Daily surveys on study days one through 16 and again on study day 28 evaluating symptoms, daily activities, and hospitalization/rehospitalization status during trial enrollment. The primary outcome was longitudinal change in an ordinal scale based on combination of symptoms, activity, and hospitalization status through Day 15 and was analyzed by use of a Bayesian longitudinal proportional odds logistic regression model for estimating the probability of a superior recovery for lopinavir/ritonavir over placebo (odds ratio [OR]>1). The primary outcome was analyzed in the intention-to-treat population and safety analyzed in the safety population of participants who received at least one dose of the allocated treatment.

15. SUBJECT TERMS- COVID-19, Antiviral, Outpatient, Lopinavir, Ritonavir, Clinical trial

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT:**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
			UU	17	Erin Anderson
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
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1.0 EXECUTIVE SUMMARY

Effective therapies for COVID-19 were urgently needed in early 2020. Lopinavir/Ritonavir (Kaletra) is an antiviral agent used to treat HIV-1 and is a potent in vitro inhibitor of SARS-CoV-2, the virus that causes COVID-19. Initial clinical data suggested possible relevance as a potential therapeutic agent early in the course of patients with COVID-19. We conducted a blinded, multicenter, placebo controlled randomized clinical trial to determine the effectiveness of Lopinavir/ritonavir 400 mg/100 mg orally twice daily for twenty-eight doses (Days 1-14) in treatment of COVID-19. We recruited 448 patients age ≥18 years with laboratory-confirmed SARS-CoV-2 infection by RT-PCR or other molecular test collected within the past 6 days. Eligible patients were randomized through a central electronic system in a 1:1 ratio, to lopinavir/ritonavir (intervention) versus placebo (control). Daily surveys on study days 1 through 16 and again on study day 28 evaluated symptoms, daily activities, and hospitalization status. The primary outcome was longitudinal change in an ordinal scale based on a combination of symptoms, activity, and hospitalization status through day 15 and was analyzed by use of a Bayesian longitudinal proportional odds logistic regression model for estimating the probability of a superior recovery for LPV/r over placebo (odds ratio >1).

2.0 INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Although the epidemiology is not fully elucidated, most adults with COVID-19 appear to experience fever, cough, and fatigue and then recover within 1-3 weeks. However, a portion of adults with COVID-19 develop severe illness, typically manifesting as pneumonia and hypoxemic respiratory failure, with continued progression to acute respiratory distress syndrome (ARDS) and death in some cases.[1–3] There is an urgent need for outpatient therapies with a demonstrated ability to improve recovery progression of COVID-19 to severe illness. Based on mechanism of action and early clinical experiences, several agents currently available in the U.S. are proposed as potential therapies to prevent disease progression.[4–6] Among these potential therapies, lopinavir/ritonavir has generated substantial interest due to antiviral and immunomodulatory activity and established safety profiles with FDA approval for use in other conditions. In this trial, we will evaluate effectiveness and safety of lopinavir/ritonavir for the early treatment of adults with COVID-19 in the outpatient setting, prior to hospitalization.

COVID-19 was first identified as a cluster of cases of pneumonia among a group of workers from a seafood wholesale market in Wuhan, China in November 2019.[7] This observation, along with subsequent viral genotyping showing significant genetic similarities to the bat coronaviruses[8] suggest a zoonotic origin, although the specific reservoir and intermediary species remain unclear.[9] The COVID-19 infection represents the seventh coronavirus known to cause disease in humans.[10] Four of the coronaviruses viruses are known to cause symptoms of the common cold in immunocompetent individuals while two others (SARS-CoV and MERS-CoV) have caused recent outbreaks of severe and sometimes fatal respiratory diseases.[11] SARS-CoV-2 appears to exploit the same cellular receptor as SARS-CoV and MERS-CoV,[12] and its severity may similarly result from a predilection for intrapulmonary epithelial cells over cells of the upper airways.[13,14]

Since the first documented human case, COVID-19 has spread exponentially with over 96 million confirmed cases and 2 million deaths worldwide as of January 19, 2021. While most patients recover after a mild, brief illness with fever and cough, the disease has a clinical spectrum ranging from asymptomatic infection[15] to ARDS and death.[16] The most common reasons for ICU care are respiratory failure and ARDS, with a minority developing shock and possibly cardiomyopathy.[17] The case fatality rate is estimated to be 0.25% to 3.0%.[18]

Limited therapies were available to improve recovery and prevent progression of COVID-19 in the outpatient setting during the first year of the pandemic. Two neutralizing monoclonal antibodies therapies, Bamlanivimab (Eli Lilly) and Casirivimab/Imdevimab (Regeneron), received Emergency Use Authorization approval from the U.S. Food and Drug Administration (FDA) based on early data suggesting reduction in viral load, symptom improvement, and prevention of hospitalization. However, the impact and military relevance of these agents were limited by: 1) only adults ≥65 years or with significant comorbidities were authorized to receive; 2) the therapies required closely monitored intravenous infusion. While these monoclonal antibody therapies demonstrated the concept that early antiviral therapy could be effective in COVID-19, **scalable oral antiviral therapy for outpatients with COVID-19 were and are desperately needed.**

This proposal directly addressed the programmatic goal of developing therapeutics for treatment of COVID-19 that can be administered outside of the hospital setting. We proposed to test a highly promising oral antiviral, lopinavir/ritonavir (FDA-approved for HIV-1 treatment), in the outpatient treatment of COVID-19 to prevent disease progression and improve recovery. The safety profile was well-established through prior HIV clinical trials and extensive post-marketing experience. Lopinavir/ritonavir has substantive *in vitro* activity against SARS-CoV-2, the virus that causes COVID-19, as well as early clinical data supporting potential efficacy in patients with COVID-19 and other severe coronaviruses. Because we leveraged a repurposed medication and our highly efficient federally-funded clinical trials networks, we proposed an advanced stage of technical readiness (TRL 6-7) through this phase III clinical trial that provided definitive results on efficacy of this antiviral therapy in a setting relevant to immediate military

application. The clinical trial was conducted with an FDA IND exemption. In addition, this infrastructure of enrolling outpatients with COVID-19 provided a structure for rapid integration of other candidate drugs in future clinical trials.

3.0 METHODS, ASSUMPTIONS AND PROCEDURES

3.1 Research Design

We conducted an investigator-initiated, multicenter, blinded, placebo-controlled, randomized clinical trial evaluating lopinavir/ritonavir vs placebo for early treatment of adults with COVID-19 in the outpatient setting prior to hospitalization.

3.2. Study Network and Sites

We conducted this trial through 12 geographically dispersed, U.S. academic medical centers in the Influenza Vaccine Effectiveness in the Critically Ill (IVY) Network. The network has a strong track record of designing and conducting high quality clinical research on pneumonia, influenza, and other respiratory viruses. All sites specialize in enrolling adults with acute infections, and recently completed studies of severe influenza and both outpatients and inpatients with COVID-19 funded by the Centers for Disease Control and Prevention (CDC). Sites also participate in the National Heart, Lung, and Blood Institute (NHLBI) Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network.

3.3 Study Design

Study Preparation:

We recruited patients who tested positive for COVID-19 and were in the outpatient setting. We accessed our own hospital's testing logs and contacted patients by telephone and email to ask about their willingness to participate. We also advertised the study to the local community and nationally through social media, as well as online advertisements. We explained the study by telephone or secure video conferencing and obtained an electronic consent (via REDCap). We did not enroll patients who lacked decision-making capacity due to logistical issues with remote study medication administration and accurate data collection. Enrolled subjects completed a daily electronic symptom log through a REDCap platform. Research personnel conducted telephone assessments as needed for monitoring safety or efficacy, to supplement electronic data collection. The research team acquired local hospital records for patients hospitalized during their trial participation to determine clinical course and outcome assessment. We obtained permission for follow-up data collection, including medical records release from outside hospitals when necessary.

Prescreening and Screening:

The site investigator or delegate screened for non-hospitalized patients with laboratory confirmed COVID-19 (that is, a positive laboratory test for SARS-CoV-2 by RT-PCR or other molecular method). The source of these patients was primarily patients seen and sent home from the enrolling hospital emergency department, urgent care, primary care, virtual care/telemedicine visits, or testing centers. We also advertised the study at outpatient testing sites and nationally via google ads and social media advertisement for self-referral to the study.

For patients who appeared to meet eligibility criteria after screening, we completed an electronic case report form to determine eligibility and track exclusions. We accessed and stored the electronic case report form in the secure electronic database. At the time of entry into the screening database, we assigned the patient a screening number.

If and when the patient appeared to meet all eligibility criteria, the site investigator or delegate approached the patient to confirm eligibility, discuss potential study recruitment, and proceed with informed consent. Most patients were no longer in the healthcare setting and, therefore, these discussions occurred primarily by telephone or videophone to the patient's home.

For all excluded patients, including refusal by the patient to participate, we collected a small number of variables, including month and year patient met screening criteria and reason(s) patient was excluded for reporting in the CONSORT diagram (Figure 1) of the manuscript. Due to the nature of this trial in the outpatient setting and for staff safety and personal protective equipment (PPE) conservation, these encounters almost always occurred via telephone or videophone.

Inclusion criteria: We defined the target population as non-hospitalized (outpatient) adults (age ≥18 years) with symptomatic COVID-19 per the following inclusion criteria:

1. Age ≥18 years
2. Laboratory-confirmed SARS-CoV-2 by RT-PCR or other molecular test within the past 6 days

3. At the time of enrollment, current symptoms of acute respiratory infection for ≤6 days, defined as one or more of the following: cough, fever, shortness of breath, chest pain, abdominal pain, nausea/vomiting, diarrhea, body aches, weakness/fatigue

The source of these patients was primarily the enrolling hospital emergency department, urgent care, primary care, or virtual care/telemedicine visits, as well as national advertising.

Exclusion criteria:

1. Prisoner
2. Pregnancy
3. Breast feeding
4. Two individuals from the same household cannot be enrolled in the study
5. Unable to randomize within 6 days after onset of acute respiratory infection symptoms
6. Hospitalization within the 6 days prior to randomization
7. Inability to swallow oral medications
8. Refusal or inability to be contacted and participate in daily symptom/safety monitoring in English or Spanish during the two-week follow-up period
9. Previous enrollment in this trial
10. Known severe chronic kidney disease requiring dialysis
11. Known liver disease (cirrhosis or >3 times upper limit of normal for AST or ALT in medical record if available)
12. Known hepatitis B or hepatitis C infection
13. Known history of jaundice
14. Current heavy alcohol use, defined as 8 drinks or more per week for women or 15 drinks or more per week for men
15. Known seizure disorder
16. Known HIV infection
17. Known history of pancreatitis
18. Known history of prolonged QT interval (Long QT Syndrome, patient report, or QTc >500 milliseconds on most recently available electrocardiogram within the past 2 years)
19. Receipt of >1 dose of lopinavir/ritonavir in the 10 days prior to enrollment
20. Known allergy to lopinavir/ritonavir
21. Current prescription (with planned continuation) or planned administration during 14-day study period of medication at high risk for QT prolongation as follows:
    a. *Antiarrhythmics:* Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, procainamide, propafenone, quinidine, sotalol
    b. *Anti-cancer:* Arsenic trioxide, oxaliplatin, vandetanib
    c. *Antidepressants:* Amitriptyline, citalopram, escitalopram, imipramine
    d. *Antimicrobials:* azithromycin, ciprofloxacin, clarithromycin, erythromycin, fluconazole, levofloxacin, moxifloxacin, pentamidine, hydroxychloroquine
    e. *Antipsychotics:* aloperidol, chlorpromazine, droperidol, olanzapine, pimozide, quetiapine, thioridazine, risperidone, ziprasidone
    f. *Others:* cilostazol, cimetidine, cisapride, donepezil, methadone, ondansetron, sumatriptan
22. Current prescription (with planned continuation) or planned administration during 14-day study period of any of the following medications: alfuzosin, apalutamide, astemizole, ergot-containing medicines (including dihydroergotamine mesylate, ergotamine tartrate, methylergonovine), lomitapide, lovastatin, lurasidone, midazolam, phenobarbital, phenytoin, ranolazine, rifampin, sildenafil, simvastatin, rivaroxaban, St. John's Wort, terfenadine, triazolam. Patients who were on warfarin or fluticasone were advised to contact their primary care provider to advise them that they were in the trial and possibly received lopinavir/ritonavir which can influence levels of either drug and may have required more frequent monitoring.

Consent:

We obtained written informed consent from the patient. We did not enroll patients who lacked decision-making capacity due to logistical issues with remote study medication administration, safety monitoring, and accurate data collection.

In-person visits for patients with known COVID-19 who were deemed stable for outpatient management and home quarantine violated infection control principles and policies. Given the infectious risk from COVID-19 and shortages of PPE, there was a moral and practical imperative to minimize face-to-face contact between patients and non-clinical personnel. Therefore, we used "no-

touch" consent procedures for this trial, employing the below electronic remote consent process to obtain written informed consent:

1. A link for the electronic consent was sent to the subject.
2. Research staff contacted the patient by telephone or videophone (method dictated by institutional policy) to have an informed consent conversation. This step confirmed subject identity.
3. If they consented, the patient signed the consent form. This was:
    a. an actual signature (traced their finger on the screen) OR
    b. a username and password specific to the individual signing

This approach complied with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300); https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent.

We provided the information for the informed consent discussion in a formal document that was approved by the IRB and in a language comprehensible to the potential participants, using an interpreter if necessary. English and Spanish documents were approved for use in this trial. The information presented in the consent form and by the research staff detailed the nature of the trial and what was expected of participants, including any potential risks or benefits of taking part. We clearly stated that the participant was free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient did not speak English, a translated Spanish consent and qualified interpreter was employed, using similar "no-touch" principles. Use of a telephone or video interpreter and the interpreter's identity was documented on the electronic consent.

After allowing the potential participant time to read the informed consent document, research staff answered any additional questions.

Randomization:

We used a central electronic randomization system to allocate participants equally among enrolling study arms with stratification by enrolling site and age (≥65 years or <65 years), given that risk for morbidity and mortality, and potential treatment response, was influenced by age. Study participants, treating clinicians, study personnel, and outcome assessors were blinded to allocation. Only the central study pharmacy and one member of the biostatistical team who prepared closed data and safety monitoring board (DSMB) reports were unblinded.

Intervention:

Participants assigned to the LPV/r arm received 400 mg/100 mg twice daily for 28 doses (14 days total). Participants assigned to the placebo group received a generic oral placebo matching the LPV/r regimen.

The study drug was prepared by a central pharmacy (Belmar Pharmacy, Golden, Colorado) to provide the randomized treatment labeled by study day. Packaging of both LPV/r and placebo was designed to blind participants to their treatment assignment; the study drug was shipped to participants using overnight delivery.

Data analysis and Statistical design:

The **primary outcome** was a modification of the WHO clinical status scale measured longitudinally through day 15, modified for use in outpatients, as follows:

1. Death
2. Hospitalized on mechanical ventilation or ECMO
3. Hospitalized on supplemental oxygen
4. Hospitalized not on supplemental oxygen
5. Not hospitalized with symptoms and limitation in activity
6. Not hospitalized with symptoms but with no limitation in activity
7. Not hospitalized without symptoms nor limitation in activity

To reflect the mild to moderate severity of disease in the outpatient setting, the modifications were to include three non-hospitalized states (no symptoms, symptoms without activity limitations, symptoms with activity limitations), three hospitalized states based on supplemental oxygen use (no supplemental oxygen, on supplemental oxygen, on mechanical ventilation or extracorporeal membrane oxygenation), or death. Using the serially collected clinical status through day 15 of the study allows the

changes over treatment to be included in the analysis of the primary outcome, rather than using a non-longitudinal summary which would obscure the trends over time.

Secondary outcomes included:

1. COVID Modified Ordinal Outcome Scale at Days 8 and 29
2. Hospitalization to Day 29
3. Time to symptom and fever resolution to Day 29
4. All-cause, all-location mortality to Day 29
5. Oxygen-free days through Day 29
6. Fever-free days through Day 29
7. Ventilator-free days through Day 29
8. Vasopressor-free days through Day 29
9. ICU-free days through Day 29
10. Hospital-free days through Day 29
11. Safety outcomes, including adverse events

Analysis Plan and Sample Size Calculations:

The primary analysis used a longitudinal proportional odds model with random intercept for each participant adjusted for the following co-variables: age, gender, and duration of acute respiratory infection symptoms prior to randomization. The proportional odds assumption was examined using graphical methods. If proportionality was clearly violated, we planned to use partial proportional odds or non-proportional odds models.

To account for non-linear effects of treatment over the course of treatment, all analyses included a restricted cubic spline with four knots and a treatment-by-time interaction. The prior for the intercept assumed a Dirichlet distribution, and the priors for all other coefficients assumed a normal distribution with a mean of 0 and SD of 10. For adjusted models, prespecified covariates were race/ethnicity, age, sex, symptom duration (in days), presence of any predefined comorbidities, receipt of monoclonal antibody treatment, vaccination status, and time period of the trial broken into 3-month quarters. With respect to missing data, the chosen Bayesian methods do not require imputation for missing time points, assuming a missing at-random assumption conditional on the baseline covariates and previous time points. ORs greater than one indicate a benefit for LPV/r.

Subgroup analyses of the primary outcome included age, sex, race/ethnicity, body mass index, baseline renal function, hypertension, diabetes mellitus, cardiovascular disease, and duration of respiratory symptoms before randomization. For each subgroup, the unadjusted model was fit, with the addition of the subgroup variable without and with interaction with treatment. To facilitate a more parsimonious approach to determining if an interaction effect may be present, Bayesian stacking was then used to compare the two models. If the model with an interaction had a posterior weight of 80% or greater from the stacking procedure, models would then be fit within the respective subgroups. Exploratory analyses evaluated the severity of each symptom included in the primary outcome using the same unadjusted model. Secondary (Table 2) and safety outcomes (Table 3) are described below.

The sample size was based on a frequentist proportional odds model with 90% power to detect an odds ratio (OR) of 1.75, assuming a 5% type I error rate. To account for an expected 10% loss to follow-up rate, 300 participants were needed per arm. The power calculation was based on limited preliminary data, given the emerging pandemic in May 2020. We prespecified interim monitoring rules for approximately 25%, 50%, and 75% of total enrollment based on the posterior probability of efficacy >95% or the posterior probability of inefficacy being >90%, with futility monitoring based on the predictive probability of success is less than 10%.

4.0 MAJOR EVENTS/MILESTONES/SUCCESS

We successfully met the following milestones:

- Data compiled and analyzed
- Abstract submission to SOMA 2023 – awaiting approval
- Primary Analysis Manuscript published

5.0 RISK ASSESSMENT

5.1 Risk Analysis

Federal regulations at 45 CFR 46.111(a)(1) require that risks to participants are minimized by using procedures which are consistent with sound research design. This trial protocol incorporated numerous design elements to minimize risk to patients that met this human subject protection requirement. Lopinavir/ritonavir is approved by the U.S. Food and Drug Administration and has been used in clinical practice for decades in a number of patient populations with an established safety profile. The dose and route of administration of this medication in this trial is comparable to the dose and route of administration approved for the treatment of other acute infections, such as HIV-1. The duration of treatment in this trial of 14 days was significantly shorter than for treatment of HIV-1 infections, for which this drug is frequently administered for multiple years. To further mitigate risk, we excluded patients with specific risk factors for adverse events and patients receiving medications that may have interacted with LPV/r.

We collected data on adverse events that were significant enough to warrant health care evaluation. The trial protocol included active monitoring of clinically significant adverse events, clinical outcomes, and interim analyses by an independent data and safety monitoring board empowered to stop or modify the trial at any time, including the need to request additional safety monitoring if determined to be warranted.

Safety Outcomes

Solicited adverse events are presented in Table. Rates were similar between LPV/r and placebo. Five (2.3%) LPV/r participants reported a severe rash vs no such reports among placebo participants. The one observed death in the LPV/r group due to COVID-19 pneumonia was adjudicated as being unrelated to the study treatment.

5.2 Technical Challenges

Enrollment Challenges: Screening and enrollment procedures took place remotely in order to reduce COVID-19 exposure to site investigator and/or research coordinator, as well as PPE conservation. The site investigator or delegate screened for non-hospitalized patients with laboratory confirmed COVID-19 online via patient Electronic Health Record or by self-report survey distributed and collected through REDCap. Infrequent technical challenges arose during REDCap or EHR down time. Additionally, COVID-19 cases rose and fell throughout the duration of this study throughout the country. Vaccine administration reduced anticipated case numbers over the course of the study, but this was not the major limiting factor in enrollment. Enrollment challenges centralized around hesitancy with the medication, potential side effects, and the low monetary compensation.

Errors with treatment administration: Lopinavir/ritonavir were administered orally and did not present major challenges for administration. If a subject encountered an error with administration of medications, they were instructed to contact research personnel with questions or seek emergency services for a severe reaction. Additionally, there were frequent errors with medical delivery due to mail service delays and limitations to delivery (i.e. coded mail box, insufficient delivery personnel, etc.).

6.0 TRANSITION PLAN

6.1 Military Relevance

The U.S. military continues to be at significant risk for COVID-19 infections and related impacts on combat readiness. Early in the pandemic saw the cancellation of nearly all domestic travel and major military exercises (Military Times 25 MAR 2020). This directly impacted deployments in Syria, Iraq, and Afghanistan, as well as strategic exercises in the Pacific and European regions. The DoD implemented Health Protection Condition (HPCON) Charlie and strict limitations on access to military installations to mitigate risks. Throughout 2020 and 2021, travel restrictions were in place at 121 of 231 DoD installations, including FT Bragg, Offutt AFB, and FT Hood. The U.S. Army deployed field hospitals to assist with civilian efforts, and the U.S. Navy deployed two hospital ships (Defense.gov 25 MAR 2020). Since the start of the pandemic, the DoD has mobilized over 7,000 doctors, nurses, and medical technicians while the MHS has shifted its research priorities to combat the coronavirus. Despite the interventions, the DoD has reported 453,456 service member, 167,988 civilian, 72,867 dependent, and 16,222 contractor COVID-19 cases, leading to 6,587 hospitalizations and 690 deaths as of December 8, 2022. The need for outpatient COVID-19 treatment remains high as new and potentially aggressive variants emerge. This study aimed to provide information needed for treatment to aid in combat readiness.

6.2 Transition Strategy

This project yielded a definitive answer on the efficacy and safety of a promising candidate therapy, **lopinavir/ritonavir**, in the early, outpatient treatment of COVID-19. While LPV/r did not prove efficacious in this clinical trial, this infrastructure was developed and

refined to rapidly test other candidate drugs of high interest to the DoD in future clinical trials in non-hospitalized patients with COVID-19 or other respiratory infections.

7.0 RESULTS

Between June 1, 2020, and December 16, 2021, 10,568 patients were assessed for eligibility, of whom 448 were randomized to receive either lopinavir/ritonavir (n=216) or placebo (n=221) and are included in the intention-to-treat analysis. The mean duration of symptoms prior to randomization was 4·3 days [SD 1·3]. There were no differences observed between treatment groups through the first 15 days for the ordinal outcome based on the primary outcome (OR 0·96; 95% CrI: 0·66 to 1·41) (Figure 2). There were 3·2% (n=7) of lopinavir/ritonavir and 2·7% (n=6) of placebo participants hospitalized by day 28 (Table 1). Serious adverse events did not differ between groups.

8.0 CONCLUSION/DISCUSSION

Early treatment of non-hospitalized patients with LPV/r within 6 days of COVID-19 symptom onset did not improve symptom resolution and hospitalization in non-hospitalized participants with COVID-19 when compared to placebo. There was no evidence that specified subgroups may benefit from the intervention. Secondary and safety outcomes were similar between groups, with a low over- all hospitalization rate of 2.9%. Through the novel, decentralized TREAT NOW platform trial, we successfully enrolled patients across the United States using just five enrolling sites, with robust intervention delivery and longitudinal data collection using a remote approach.

TREAT NOW included other innovations worth noting. The use of daily, longitudinal data collection with Bayesian modeling for the primary outcome analysis facilitated the estimation of missing responses and the ability to use an ordinal scale reflecting a range of participant outcomes over time. Given the desire to reduce contact of study personnel and expand the reach of trial recruiting of non-hospitalized COVID-19 individuals, our study leveraged the ability to remotely enroll and manage participants through the fully decentralized approach. This allowed greater flexibility for participants across the United States since each TREAT NOW site could serve as an enrolling center for non-local participants. Additionally, the use of a central pharmacy with overnight shipping of allocated treatment doses removed the requirement for participants to attend a study site to obtain the investigational drug. Finally, we implemented automated daily surveys to track symptom resolution, safety, and disease progression, which reduced patient-coordinator contact unless necessary for follow-up (i.e., non-response notification, AE trigger). We constructed the surveys to be brief and mobile-friendly to encourage daily participation, which adds validity and power to the outcome assessment. Accordingly, over 83% of potential daily data collection was completed with this approach (Appendix Figure 4). The decentralized nature allowed for targeted advertising via social media to further increase enrollment and representation across a wide range of geographic and socioeconomic groups. The TREAT NOW platform also served as a model for the ongoing ACTIV-6: COVID-19 Study of Repurposed Medications platform trial (NCT04885530).

9.0 DELIVERABLES

9.1 Publications

Abstract Title: Kaizer AM, Wild J, Lindsell CJ, et al. Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19: a summary of the protocol and analysis plan for a decentralized randomized controlled trial. *Trials*. 2022;23(1):273. Published 2022 Apr 8. doi:10.1186/s13063-022-06213-z

Manuscript: Kaizer AM, Shapiro NI, Wild J, et al. Lopinavir/ritonavir for treatment of non-hospitalized patients with COVID-19: a randomized clinical trial [published online ahead of print, 2022 Dec 27]. *Int J Infect Dis*. 2022;128:223-229. doi:10.1016/j.ijid.2022.12.028

9.2 Presentations

Presentation Title: Kaizer AM, Shapiro NI, Wild J, et al. Lopinavir/ritonavir for treatment of non-hospitalized patients with COVID-19: a randomized clinical trial.

Conference: Submitted to Special Operations Medical Scientific Assembly, awaiting approval

10.0 COST

Salary & Benefits	**$ 215,882.11**
Subcontracts	**$ 1,089,769.69**
Other Costs	**$ 113,566.10**
F&A	**$ 108,102.57**
Total	**$ 1,527,320.47**

11.0 REFERENCES

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TABLES AND FIGURES

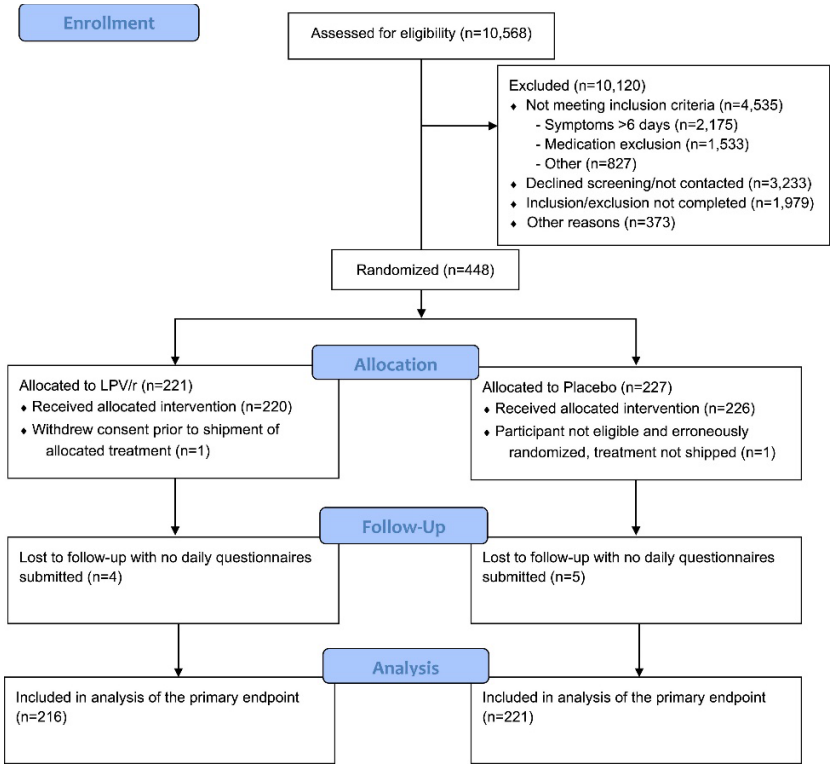

Figure 1. CONSORT Diagram

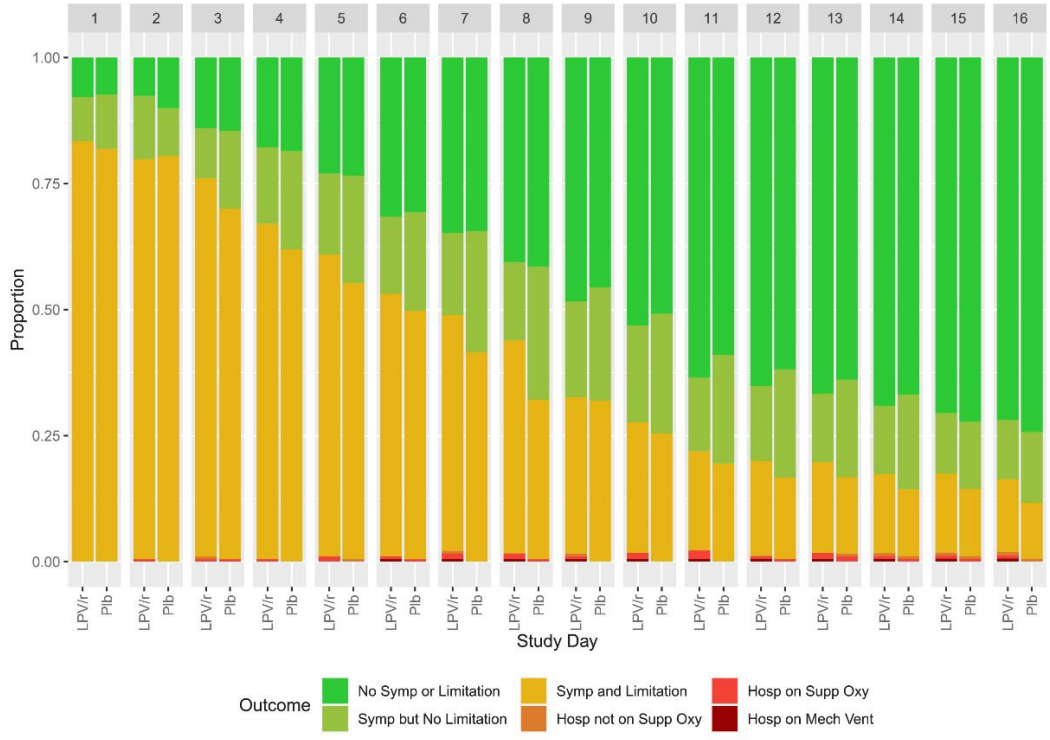

Figure 2. COVID-19 ordinal outcome by study arm and study day. The unadjusted OR that LPV/r results in a better ordinal category than Plb over the first 15 days after randomization was 0.97 (95% credible interval: 0.67 to 1.40; Pr[OR >1] = 0.44), representing no significant improvement over the course of 15 days. Hosp, hospitalization; LPV/r, lopinavir/ritonavir; Mech Vent, mechanical ventilation; OR, odds ratio; Plb, placebo; Supp Oxy, supplemental oxygen; Symp, symptoms.

Table 1. Baseline characteristics of the overall cohort

Characteristics	Lopinavir/ritonavir (N = 220)	Placebo (N = 226)
Age (years), mean (SD)	39.9 (12.2)	41.7 (12.2)
Female sex, n (%)	129 (58.6%)	132 (58.4%)
Race/ethnicity, n (%)[a]		
Non-Hispanic White	170 (77.3%)	184 (81.4%)
Non-Hispanic Black	19 (8.6%)	16 (7.1%)
Non-Hispanic other	8 (3.6%)	10 (4.4%)
Hispanic	20 (9.1%)	13 (5.8%)
Missing	3 (1.4%)	3 (1.3%)
Body mass index (kg/m^2), mean (SD)	29.3 (7.8)	27.9 (6.8)
Number of comorbidities, n (%)[b]		
0	46 (20.9%)	53 (23.5%)
1	86 (39.1%)	85 (37.6%)
≥2	88 (40.0%)	88 (38.9%)
Number of baseline symptoms, n (%		
1	13 (5.9%)	9 (4.0%)
2	25 (11.4%)	25 (11.1%)
3	48 (21.8%)	42 (18.6%)
4	45 (20.5%)	54 (23.9%)
5	32 (14.5%)	26 (11.5%)
≥6	57 (25.9%)	70 (31.0%)
Symptom duration (days), mean (SD	4.3 (1.3)	4.2 (1.3)
Vaccination status, n (%)[d]		
Fully vaccinated	45 (20.5%)	48 (21.2%)
Partially vaccinated	17 (7.7%)	21 (9.3%)
Not vaccinated	109 (49.5%)	109 (48.2%)
Unknown	49 (22.3%)	48 (21.2%)

a Race/ethnicity as reported by participant.

b Comorbidities include class 1-3 obesity, hypertension, coronary artery disease, asthma, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, liver disease, immunosuppressive condition, rheumatologic/autoimmune condition, neurological condition, or blood disorder.

c Baseline symptoms include weakness/fatigue, cough, body aches, fever, shortness of breath, diarrhea, chest pain, nausea, and abdominal pain.

d Full vs partial vaccination status based on approved number of doses, not vaccinated represents participants enrolled before approved vaccines or reporting not being vaccinated, unknown represents period in trial between vaccine approval and when data was collected on vaccine status.

Table 2. Secondary Outcomes

Outcome	Lopinavir/ritonavir (N = 220)	Placebo (N = 226)
Worst ordinal score over first 15 days		
1: Death	0 (0.0%)	0 (0.0%)
2: Hospitalized on mechanical ventilation/extracorporeal membrane oxygenation	1 (0.5%)	0 (0.0%)
3: Hospitalized on supplemental oxygen	5 (2.3%)	4 (1.8%)
4: Hospitalized not on supplemental oxygen	1 (0.5%)	2 (0.9%)
5: Not hospitalized with symptoms & limitations	187 (86.6%)	191 (86.4%)
6: Not hospitalized with symptoms, no limitations	10 (4.6%)	14 (6.3%)
7: Not hospitalized without symptoms nor limitations	12 (5.6%)	10 (4.5%)
Missing	4	5
All-cause mortality through day 29, n (%)	1 (0.5%)	0 (0.0%)
Hospitalized through day 29, n (%)	7 (3.2%)	6 (2.7%)
Time to hospitalization (days), median (Q1, Q3)	6.0 (4.0, 8.0)	7.0 (5.2, 11.0)
Time to symptom resolution (days), median (Q1, Q3)	11.0 (8.0, 29.0)	11.0 (7.0, 29.0)
Missing	12	5

Table 3. Adverse Events

Symptom	Lopinavir/ritonavir (N = 220)	Placebo (N = 226)
Serious AEs	2 (0.9%)	1 (0.4%)
Protocol-specified AEs		
Seizures	0 (0.0%)	0 (0.0%)
Heart palpitations	12 (5.5%)	15 (6.6%)
Pancreatitis	0 (0.0%)	0 (0.0%)
New kidney problems	0 (0.0%)	1 (0.4%)
Hypoglycemia	3 (1.4%)	2 (0.9%)
Severe skin reaction	5 (2.3%)	0 (0.0%)
Anemia/liver problem/low platelet	3 (1.4%)	3 (1.3%)
Respiratory failure	1 (0.5%)	0 (0.0%)

12.0 List of Symbols, Abbreviations and Acronyms

AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
CDC	Center for Disease Control
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
DCC	Data Coordinating Center
DoD	Department of Defense
DSMB	Data safety monitoring board
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report forms
EHR	Electronic Health Record
EKG	Electrocardiogram
EUA	Emergency Use Authorization
FDA	Food & Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPCON	Health Protection Condition
ICU	Intensive care unit
ID	Identification
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
IVY Network	Influenza Vaccine Effectiveness in the Critically Ill Network
KDIGO	Kidney Disease Improving Global Outcomes
LFT	Liver function test
LPV/r	Lopinavir/ritonavir
MERS-CoV	Middle East respiratory syndrome coronavirus 2
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
PETAL Network	Prevention and Early Treatment of Acute Lunch Injury Clinical Trials Network
PI	Principal investigator (a clinician responsible for one site)
PPE	Personal protective equipment
QTc	QT interval corrected for heart rate
REDCap	Research Electronic Data Capture
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sIRB	Single IRB
SUSAR	Suspected unexpected serious adverse reaction
US	United States
VCC	Vanderbilt Coordinating Center
WHO	World Health Organization