Miami Cardiac and Vascular Institute
Clinical Research Protocol

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Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients with COVID-19 (COLHEART-19)

Protocol Number:	COLHEART-19 Version 2.0
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Development Phase:	Phase 2
Sponsor/Investigator:	Sandra Chaparro, MD
Funding Organizations:	Miami Cardiac and Vascular Institute
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Approval:

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Title: Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients with COVID-19 (COLHEART-19)

Protocol Date: 06/05/2020

_____ _____

Investigator Signature *Date*

Sandra Chaparro, MD

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Contents

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BNP	brain naturetic peptide
BUN	blood urea nitrogen
CrCL	creatinine clearance
CRP	C-reactive protein
DMC	Data Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IRB	Institutional Review Board
IV	intravenous
PI	Principal Investigator
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients with COVID-19 **(COLHEART-19)**
SPONSOR/INVESTIGATOR	Miami Cardiac and Vascular Institute(MCVI), Baptist Hospital Name: Sandra Chaparro, MD Telephone: 786-596-3505 Fax: 786-533-9570 E-mail: sandrach@baptisthealth.net
FUNDING ORGANIZATIONS	Miami Cardiac and Vascular Institute
NUMBER OF SITES	Single Center Miami Cardiac and Vascular Institute, Baptist Hospital
RATIONALE	Myocardial injury has been described in up to 30% of COVID-19 infected patients, and portends a poor prognosis with currently no known treatment. Colchicine is a widely available, well-established, inexpensive, oral anti-inflammatory agent that has been FDA approved for the treatment of inflammatory disorders including gout and familial Mediterranean Fever. Trials have also shown its benefit to prevent post-cardiotomy syndrome, to treat acute and recurrent pericarditis, and reduce cardiovascular events after myocardial infarction. We extrapolate based on these indications and studies that colchicine may also help improve outcomes in hospitalized COVID-19 patients with evidence of cardiac injury.
STUDY DESIGN	Open-label (unblinded) randomization to treatment of colchicine plus current care per institution treating physicians vs. current care per institution treating physicians (control arm)
PRIMARY OBJECTIVE	To determine if Colchicine improves short-term outcomes in hospitalized COVID-19 patients with cardiac manifestations of disease.
SECONDARY OBJECTIVES	To assess if Colchicine reduces additional indices of cardiac injury in hospitalized COVID-19 patients with cardiac manifestations of disease
NUMBER OF SUBJECTS	75

SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Men and Women ≥ 18 years of age 2. Admission to hospital and respiratory status indicating oxygen therapy and/or mechanical ventilation. 3. Cardiac injury (**any of the following**) a. Elevated troponin level b. Elevated BNP level c. New ischemic or arrhythmogenic ECG/telemetry changes d. New decrease in LVEF or new pericardial effusion on echocardiogram 4. Able to provide informed consent Exclusion Criteria: 1. Requirement of immediate need for mechanical ventilation and or circulatory support. 2. Pregnancy, breastfeeding mothers, and women of childbearing age who are unable to use adequate contraception, which includes: a. Intrauterine devices (IUD), contraceptive implants, or tubal sterilization b. Hormone method with a barrier method c. Two barrier methods d. If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must also be used in conjunction 3. History of severe hematologic or neuromuscular disorder 4. Co-administration of CYPA3A4 and P-glycoprotein transport inhibitor 5. Severe renal impairment with concomitant hepatic impairment 6. Concurrent use of colchicine and strong or P-glycoprotein inhibitor with renal or hepatic impairment
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Colchicine dosing = 0.6 mg bid x 30 days Decrease dose to 0.3-0.6 mg daily or every other day in setting of gastrointestinal intolerance (nausea, diarrhea, emesis, abdominal discomfort) Decrease dose to 0.6 mg daily in the setting of weak or moderate CYP3A4 inhibitor Decrease dose to 0.3 mg daily in the setting of strong CYP3A4, P-glycoprotein inhibitors, or protease inhibitors Decrease dose to 0.3 mg daily in the setting of CKD stage ≥ 4 (CrCl ≤ 30 ml/min) or liver failure (AST/ALT > 3x normal). Decrease dose to 0.6 mg every 14 days in patients with end stage renal disease (ESRD) or requiring dialysis

	Route of Administration: oral
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Current care per treating physicians.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 90 days **Treatment:** 30 days • 0.6 mg po bid x 30 days **Follow-up:** The follow-up period for a study participant will be 90 days. The total duration of the study is expected to be up to 12 months.
CONCOMMITANT MEDICATIONS	All dose adjustments per manufacturer guidelines. Dose adjustments to 0.6 mg po daily in the presence of a weak or moderate CYP3A4 inhibitor, and 0.3 mg in the setting of a strong CYPA3A4 inhibitor, a P-glycoprotein inhibitor, or protease inhibitor.
EFFICACY EVALUATIONS	N/A
PRIMARY ENDPOINT	Composite of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support (MCS) at 90 days
SECONDARY ENDPOINTS	• Time (days) to the primary end point • Individual components of the primary endpoint • Peak troponin level • Delta (change from baseline to peak) troponin level • Baseline BNP level • Inflammatory biomarkers (baseline and delta CRP and D-Dimer) • Hospital length of stay • 90-day re-hospitalization
SAFETY EVALUATIONS	Reporting to regulatory bodies (MCVIIRB, FDA) will only be required for serious adverse events judged by the treating physician and study investigators to be potentially related to the administration of the study drug. All other adverse events will be reviewed by the study investigators and reported per FDA and IRB regulations.
PLANNED INTERIM ANALYSES	When approximately 25% of patients have completed the study, an interim analysis for safety will be conducted by the study investigators. Serious adverse events will be monitored by the study committee on an ongoing basis throughout the study. Serious adverse events will be reported to the Baptist Health South Florida (BHSF) IRB and FDA.
Statistical Analysis Plan	Appropriate data analysis sets will be defined. The intent-to-treat (ITT) analysis set will be used in the analyses of the primary and secondary endpoints. The ITT analysis set will include data from all subjects who are randomized, with study drug assignment designated to initial randomization, regardless of whether subjects receive any study drug or receive a different regimen from that to which they were randomized. A safety analysis set will comprise data from subjects who receive at least one dose of study drug, with treatment regimen assignment (Colchicine or control) designated

	according to the actual regimen received. Per-Protocol (PP) analysis set will be used for sensitivity analysis for the primary and secondary endpoints. The primary endpoint is the composite event rate of all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days. Fisher's exact test will be used to compare the proportion of patients achieve the composite event between two study arms. For each arm, the proportion of patients achieve the composite event at 90 days will be calculated, along with the 95% exact confidence interval. For the secondary endpoints: 1) Time (days) to the primary end point: Kaplan Meier estimates will be provided for each study arm and presented graphically. Log-rank test will be used to compare the event curves between study arms. Hazard ratios and corresponding 95% CIs will be presented. 2) Individual components of the primary endpoint, and 90-day re-hospitalization: For each of these, Fisher's exact test will be used to compare the event rate between two study arms. For each arm, the proportion of patients achieve the composite event at 90 days will be calculated, along with the 95% exact confidence interval. 3) Peak troponin level, Delta (change from baseline to peak) troponin level, Baseline BNP level, Inflammatory biomarkers (baseline and delta CRP and D-Dimer), Hospital length of stay: For each of these, unpaired t test or Wilcoxon rank rum test will be used to compare the two study arms. For each arm, descriptive statistics such as mean, median, standard deviation, IQR will be summarized and reported. Safety Analysis: Safety profile including AE and SAEs will be reported. Simple descriptive statistics will be used to summarize toxicities in terms of type, severity and minimum or maximum values for laboratory measures, time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects. Safety Analyses will be performed on Safety Analysis Set.
Rationale for Number of Subjects	This is an open-label, randomized controlled study with the primary objective to determine if Colchicine improves short-term outcomes in hospitalized COVID-19 patients with cardiac manifestations of disease. Patients will be randomized in 1:1 ratio to receive colchicine 0.6 mg po BID x 30 days plus current care per treating physicians versus current care per physicians alone (control arm). The primary endpoint is the composite event rate of all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days. Sixty-eight patients per arm are needed to achieve 80% power to detect **20**% difference in this composite event rate between the two groups, assuming 1**0**% in the treatment group and 30% event rate in the control group, with a two-sided **Fisher's exact test** at a 0.05 significance level.

	Accounting for 9% attrition rate, a total of 150 subjects (n=75 per arm) will be enrolled.

1 BACKGROUND

SARS-CoV-2, a novel betacoronavirus that causes a new human disease referred to as COVID-19, has led to a worldwide pandemic affecting over a million people to date. Of those patients infected, up to 80% have only mild symptoms that resolve spontaneously.[1] Patients that develop more severe symptoms are generally hospitalized and can experience acute respiratory distress, cardiac injury or shock, renal failure, and ultimately death.[2] Patients with underlying cardiovascular disease and elevated cardiac biomarkers are at increased risk with mortality reaching up to 70%.[3,4] While several mechanisms have been postulated for how SARS-CoV-2 may damage the heart, it is plausible that the indirect damage from innate, cellular, or humoral immune response including 'cytokine storm' may play a pivotal role.[5] We hypothesize that Colchicine may attenuate the cardiac injury observed in later stages of COVID-19 through downregulation of the inflammatory and the host adaptive immune response.

1.1 Overview of Non-Clinical Studies

Colchicine is a microtubule inhibitor and anti-inflammatory agent.[6] It has been suggested that the inhibition of the microtubule polymerization interferes with lipopolysaccharides resulting in the down-regulation of interleukin (IL) - 6, IL-1, GM-CSF, and the NLRP3 inflammasome.[7] Study of the COVID-19 inflammatory cascade shows $CD4^+$T lymphocytes rapidly activated to pathogenic T helper (Th1) cells that generate granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as cytokines that induces inflammatory $CD14^+$ and $CD16^+$ monocytes with high expression of IL-6.[8] Clinically, there is a marked increase in C-reactive protein (CRP), aspartate transaminases (AST), alanine transaminases (ALT), and decreased lymphocytes, reflecting the pro-inflammatory state.[9] Plasma troponin levels have been shown to be associated with a significant increase in CRP levels, which is associated with increased cardiac injury and mortality.[10]

1.2 Overview of Clinical Studies

Colchicine has been FDA approved for gout and familial Mediterranean fever.[7] Several studies have shown benefit in acute and recurrent pericarditis and post-cardiotomy, and more recently post-myocardial infarction.[11-15] Microtubule inhibition may also interfere with the viral replication machinery by disrupting the cellular cytoskeleton, and colchicine in viral myocarditis has been shown to improve left ventricular ejection fraction after treatment.[16,17] We extrapolate from these studies, that colchicine may benefit hospitalized COVID-19 patients with evidence of cardiac injury.

2 STUDY RATIONALE

Cardiac injury has been described in up to 30% of COVID-19 infected patients, and portends a poor prognosis with currently no known treatment. Colchicine is a widely available, well-established, inexpensive, oral anti-inflammatory agent that may help reduce myocardial injury in hospitalized patients with COVID-19.

2.1 Risk / Benefit Assessment

The most common adverse event with colchicine is gastrointestinal intolerance (diarrhea, emesis, nausea, abdominal discomfort) leading to discontinuation in 5-8% of patients. Myelosuppression and aplastic anemia are rare at the proposed dosages. Neuromuscular toxicity has been documented at an increased risk with drugs inhibitor P-glycoprotein. Taking into account there is no known treatment to prevent or treat myocardial injury in COVID-19 patients, we feel the benefits of the medication outweigh its relatively small risks.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess if Colchicine improves short-term outcomes in hospitalized COVID-19 patients with cardiac manifestations of disease. The primary endpoint is the composite of all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days.

3.2 Secondary Objectives

- To assess whether or not Colchicine reduces additional indices of cardiac injury in hospitalized COVID-19 patients with cardiac manifestations of disease

4 STUDY DESIGN

4.1 Study Overview

We propose a single center, open-label (unblinded) randomized controlled trial. Patients will be randomized in a 1:1 ratio to receive Colchicine 0.6 mg po BID x 30 days plus current care per treating physicians versus current care per treating physicians alone (control arm). Importantly, this trial design allows for patients in either study arm to receive other investigational drugs for COVID-19 as new science emerges. The primary endpoint is the composite of all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days. Secondary endpoints include time (days) to the primary end point, the individual components of the primary endpoint, other markers of cardiac injury (peak and delta troponin and baseline BNP), inflammatory biomarkers (baseline and delta CRP and D-Dimer levels), and 90-day re-hospitalization. The treatment duration will be 30 days with a 90-day follow-up period.

Inclusions/exclusion criteria will be reviewed to determine patient eligibility.

The method of permuted block randomization will be used. Permuted block sizes are not disclosed to the study personnel to minimize the likelihood of their being able to predict the next randomization assignment in the series. Eligible participants will be assigned in 1:1 ratio to an unblinded fashion to one of the following dosing regimens:

- Colchicine at 0.6 mg po bid for 30 days
- Dose reductions in the setting of concomitant CYP3A4 and P-glycoprotein inhibitors, in the setting of severe renal and hepatic disease, or if GI symptoms occur. Total duration of subject participation will be 30 days treatment followed by a 90 days follow-up period. Total duration of the study is expected to be 12 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint is the composite of all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days.

5.2 Secondary Efficacy Endpoints

Secondary endpoints include: time (days) to the primary end point, the individual components of the primary endpoint, re-hospitalization rates at 90 days, markers of cardiac injury (peak troponin, delta troponin, baseline BNP levels, inflammatory biomarkers (baseline and delta CRP and D-Dimer levels).

5.3 Safety Evaluations

Several adverse events are known with colchicine and will be monitored and include:

- Blood dyscrasia such as myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia and aplastic anemia have been reported with colchicine and will be monitored
- Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients are at increased risk, and will be monitored more closely.
- The most common adverse reactions reported in clinical trials with colchicine were gastrointestinal trace adverse effects, occurring in up to 5-8% of patients given therapeutic doses. Typical symptoms include cramping, nausea, diarrhea, abdominal pain, and emesis. These events will warrant dose-reduction and close monitoring.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of COVID-19 who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Age ≥ 18 years of age.
2. Documentation of SARS-CoV2-19 infection
3. Admission to hospital and respiratory status indicating oxygen therapy and/or mechanical ventilation.
4. Cardiac injury (any of the following):
    a. Elevated troponin level
    b. Elevated BNP level
    c. New ischemic or arrhythmogenic changes on ECG/telemetry

d. New drop in LVEF or pericardial effusion on echocardiogram

5. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Requirement of immediate need for mechanical ventilation and or circulatory support.
2. Pregnancy, breastfeeding mothers, or women of childbearing age unable to take adequate birth control during the duration of the study, which includes:
   a) Intrauterine devices (IUD), contraceptive implants, or tubal sterilization
   b) Hormone method with a barrier method
   c) Two barrier methods
   d) If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must also be used in conjunction
2. History of severe hematologic disease or neuromuscular disorders
3. Co-administration of CYP3A4 and P-glycoprotein inhibitor (i.e. Clarithromycin)
4. Severe renal impairment with concomitant hepatic impairment.
5. Concurrent use of colchicine and strong CYP3A4 or P-gp inhibitors in patients with renal or hepatic impairment

7 CONCURRENT MEDICATIONS

Patients are randomized 1:1 to colchicine 0.6 mg bid x 30 days to colchicine plus current care per treating physicians versus current care per treating physicians alone (control arm). This trial design allows for patients in either study arm to receive other investigational drugs for COVID-19 in addition to colchicine as new science emerges.

7.1 Allowed Medications and Treatments

Standard therapy for colchicine is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Eligible participants will include hospitalized patients ≥ 18 years-old with confirmed COVID-19 infection and objective evidence of cardiac injury (elevated troponin level, elevated BNP level, new ECG/telemetry changes consistent with ischemia or arrhythmia, or new drop in LVEF or new pericardial effusion on echocardiogram). Patients will be randomized in an unblinded 1:1 ratio to receive colchicine

0.6 mg po BID x 30 days plus current care per treating physicians versus current care per physicians alone (control arm).

8.2 Blinding

Study subjects are randomly assigned to colchicine plus current care per physicians versus current care per physicians (control arm). Neither the patient nor the treatment team or study investigators will be blinded. This trial design allows colchicine to be added to other investigational drugs for COVID-19 as new data and studies are available.

8.3 Formulation of Test

Colchicine is an alkaloid chemically described as (S)N- (5,6,7,9-tetrahydro- 1,2,3, 10-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide with a molecular formula of $C_{22}H_{25}NO_6$ and a molecular weight of 399.4. The structural formula of colchicine is given below.

Colchicine occurs as a pale yellow powder that is soluble in water.

COLCRYS (colchicine, USP) tablets are supplied for oral administration as purple, film- coated, capsule-shaped tablets (0.1575" × 0.3030"), debossed with "AR 374" on one side and scored on the other, containing 0.6 mg of the active ingredient colchicine USP. Inactive ingredients: carnauba wax, FD&C blue #2, FD&C red #40, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, sodium starch glycolate, titanium dioxide and triacetin.

8.3.1 Packaging and Labeling

Colchicine used for investigational purposes in COVID-19 patients will be labeled clearly and administered separately from normal medications. On discharge, a bottle clearly labeling the medication as investigational will be dispensed to the patient.

8.4 Supply of Study Drug at the Site

Colchicine will be stored per manufacturer guidelines, dispensed, and accounted for by the Baptist Hospital investigational pharmacy.

8.4.1 Dosage/Dosage Regimen

Colchicine will be administered at 0.6 mg po every 12 hours. Patients under the age of 18, pregnant breastfeeding, or women of childbearing age who are unable to take 2 forms of contraception will be excluded from the study. All dosage adjustments below per manufacturer recommendations:

1. Renal impairment:
    a. Colchicine is excreted in the urine in healthy subjects, and clearance is decreased in patients with impaired renal function.
    b. For patient with CrCL $\leq$ 30, the dose will be adjusted to 0.3 mg daily
    c. In patients with end-stage renal disease or undergoing dialysis the dose will be reduced to 0.6 mg every 14 days

2. Hepatic impairment
    a. The clearance of colchicine may be significantly reduced and plasma half-life prolonged in patient's hepatic impairment
    b. Dose will be adjusted to 0.3 mg daily for severe hepatic dysfunction (AST/ALT ≥ 3x baseline).
3. Dose adjustments for concomitant medications
    a. Strong CYP3A4 inhibitors (Atazanavir, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin
        i. Dose reduction to 0.3 mg once daily
    b. Moderate CYP3A4 inhibitors (Amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil)
        i. Dose reduction to 0.6 mg once daily
    c. P-glycoprotein inhibitors (Cyclosporin, ranolazine)
        i. Dose reduction to 0.3 mg once daily
    d. Protease inhibitors (atazanavir sulfate, darunavir)
        i. Dose reduction to 0.3 mg once daily
        ii. Colchicine should not be dispensed concomitantly with protease inhibitor in the setting of renal or hepatic impairment
    e. Strong CYP3A4 inhibitor and P-Glycoprotein inhibitor
        i. Colchicine should not be administered in the setting of both a CYP3A4 and P-Glycoprotein inhibitor such as Clarithromycin

Colchicine interacts with the P-glycoprotein transporter, and the CYP3A4 enzyme involved in drug and toxin metabolism. Fatal drug interactions have occurred when colchicine was taken with other drugs that inhibit P-glycoprotein and CYP3A4.

Avoid taking macrolide antibiotics (erythromycin or clarithromycin), ketoconazole or cyclosporine,

Avoid taking atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, grapefruit juice and atorvastatin/rosuvastatin.

8.4.2 Dispensing

Colchicine will be dispensed by the Baptist Hospital investigational pharmacy.

8.4.3 Administration Instructions

Colchicine will be prepared per the Baptist Hospital investigational pharmacy protocol~~. The medication will be dispensed by the investigational pharmacy as single doses to study participants while admitted~~. The medication will be dispensed by the Baptist Hospital Pharmacy as a completed study course-supply and will be taken as a single doses by study participatns while admitted. On discharge, the study drug will be dispensed with clear instructions to complete a 30-day course. ~~Colchicine will be prepared per the Baptist Hospital investigational pharmacy protocol. On discharge, the study drug will be dispensed with clear instructions to complete a 30-day course.~~

8.5 Supply of Study Drug at the Site

Study drug will be supplied by the Baptist Hospital investigational pharmacy through hospital protocol.

8.5.1 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be captured as a deviation. Subjects will be instructed to store the medication in original packaging (foil pouch and protected from light) at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any symptoms or adverse events. If the patient misses a dose, he/she will be instructed to document the event, but continue treatment with the next scheduled dose. Subjects will be instructed to not make up the dose. Appendix 2

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented throughout the study. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (age, sex, race) will be recorded at enrollment.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying cardiovascular disease and risk factors for cardiovascular disease will be recorded at screening.

9.1.4 Vital Signs

Body temperature, blood pressure, pulse, and respiratory rate will be performed and recorded.

9.1.5 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Inflammatory markers

Blood will be obtained and sent to the clinical lab for serum C-reactive protein (CRP) and D-Dimer on day 1 (baseline); days 3 and 7 only if the patient remains hospitalized (will avoid as an outpatient to minimize risk of COVID-19 transmission to health care workers and limit PPE use as well as to adhere to 2-week quarantine guidelines for COVID-19+ patients. Additional labs may be checked by the treating physicians as part of clinical care. Labs for a specific time period can be obtained within ±1 day of the assigned time.

9.2.2 Troponin and BNP

Blood will be obtained and sent to the clinical lab for serum troponin and BNP on days 1 (baseline); days 3 and 7 only if the patient remains hospitalized. Additional labs may be checked by the treating physicians as part of clinical care. Labs for a specific time period can be obtained within ±1 day of the assigned time.

10 STUDY SCHEMA

10.1 Screening/Enrollment Day 1 (Baseline)

1. Assess potential subjects admitted to Baptist Hospital based on inclusion/exclusion criteria
2. For patients who meet inclusion/exclusion criteria, the investigator team will review the study with the subject (or subject's legal representative) in person or over the phone and obtain written/telephone informed consent and HIPAA authorization and assent, if appropriate.
3. Assign the subject a unique screening number.
4. Record demographic data.
5. Record medical history.
6. Record concomitant medications.
7. Perform and record vital signs.
8. Record results of blood pressure testing.

9. Obtain blood samples for baseline troponin, BNP, CRP, and D-dimer levels
10. Obtain baseline echocardiogram, , which can be obtained within ±3 day of the assigned time
11. Randomize subject, dispense study drug if randomized to the colchicine arm
12. Calculate the WHO Scale and record.

10.2 Days 3 and 7 (only if the patient remains hospitalized)

1. Record any adverse events and/or review subject diary for symptoms, adverse events, and medication adherence.
2. Concomitant medications reviewed.
3. Obtain blood sample for clinical laboratory tests (troponin, BNP, D-Dimer, CRP)

10.3 Day 30 and Day 90

At 30 Days record the WHO Ordinal Scale Score and then calculate Delta Score by subtracting 30 days score minus baseline. Obtain information via telephonic interview and review of electronic medical records.

AT 90 Days record any adverse events and/or review subject diary for symptoms, adverse events, and hospitalizations via telephonic interview and review of electronic medical records. The COLHEART-19 Day Questionnaire will be used which includes the WHO Ordinal Scale in order to assess the Primary Outcome.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in

the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug
The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization

- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

All SAEs that occur (whether or not related to study drug) will be reported per Baptist Health South Florida IRB guidelines and policy. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/), the site investigator will report SAEs to the IRB and FDA.

11.3 Medical Monitoring

Sandra Chaparro, MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Name: Sandra Chaparro, MD

Phone: 786-596-3505 or 786-204-4201

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the sponsor/investigator, or study team determines that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not adherent with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Loss to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test or women of childbearing age who can no longer take adequate contraception, which includes:
    - Intrauterine devices (IUD), contraceptive implants, or tubal sterilization
    - Hormone method with a barrier method
    - Two barrier methods

- If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must also be used in conjunction

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be recorded in the study.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the sponsor/investigator, or the study team determines that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to the 30-day visit) should have an early discontinuation visit if they have been discharged from the hospital. Refer to Section 10 for early termination procedures. Subjects who withdraw after discharge from the hospital but prior to day 30 should be encouraged to come in for a final laboratory and imaging visit.

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.
Subjects who withdraw from the study itself will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. tThe form will be sent to the BHSF IRB and a copy will be filed in the site's regulatory binder.

14 STATISTICAL METHODS AND CONSIDERATIONS

14.1 General Considerations

Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. \Data Sets Analyzed

- Intent-to-Treat (ITT) Analysis Set

The ITT analysis set includes all subjects who are randomized regardless of whether subjects receive any study drug(s), or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization. This analysis set will be used in the analysis for the primary endpoint and the secondary endpoint.

- Per-Protocol (PP) Analysis Set

The PP analysis set includes data from subjects in the ITT analysis set who meet the general criteria defining the target population for this study, are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Treatment assignment will be designated according to the actual treatment received. The PP analysis set will be used in sensitivity analyses of the primary and secondary endpoints.

- Safety Analysis Set

A safety analysis set will include data from subjects who receive at least one dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set will be used in the analyses of safety variables as well as study treatment administration.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be included: race, sex, age, BMI, medication history, co-morbidities including cardiovascular disease and risk factors for cardiovascular disease.

14.3 Analysis of Primary Endpoint

The primary endpoint is the composite event rate of all-cause mortality, need for mechanical ventilation, or need for MCS at 90 days. Fisher's exact test will be used to compare the proportion of patients achieve the composite event between two study arms. For each arm, the proportion of patients achieve the composite event at 90 days will be calculated, along with the 95% exact confidence interval.

14.4 Analysis of Secondary Endpoints

Secondary endpoint: Time (days) to the primary end point Kaplan Meier estimates will be provided for each study arm and presented graphically. Log-rank test will be used to compare the event curves

between study arms. Hazard ratios and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

- Secondary endpoints: Individual components of the primary endpoint. For each of these, Fisher's exact test will be used to compare the event rate between two study arms. For each arm, the proportion of patients achieve the composite event at 90 days will be calculated, along with the 95% exact confidence interval.
- Secondary endpoints: Peak troponin level, Delta (change from baseline to peak) troponin level, baseline BNP level, Inflammatory biomarkers (baseline and delta CRP and D-Dimer), Hospital length of stay
- For each of these, unpaired t test or Wilcoxon rank rum test will be used to compare the two study arms. For each arm, descriptive statistics such as mean, median, standard deviation, IQR will be summarized and reported.

14.5 Analysis of Safety

Safety profile including AE and SAEs will be reported. Simple descriptive statistics will be used to summarize toxicities in terms of type, severity and minimum or maximum values for laboratory measures, time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects. Safety Analyses will be performed on Safety Analysis Set.

14.6 Sample Size Justification

This is an open-label, randomized controlled study with the primary objective to determine if Colchicine improves short-term outcomes in hospitalized COVID-19 patients with cardiac manifestations of disease. Patients will be randomized in 1:1 ratio to receive colchicine 0.6 mg po BID x 30 days plus current care per treating physicians versus current care per physicians alone (control arm). The primary endpoint is the composite event rate of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support (MCS) at 90 days. 68 patients per arm are needed to achieve 80% power to detect 20% difference in this composite event rate between the two groups, assuming 10% in the treatment group and 30% event rate in the control group (based on recent published studies[18,19,20]), with a two-sided Fisher's exact test at a 0.05 significance level. Accounting for 9% attrition rate, a total of 150 subjects (n=75 per arm) will be enrolled.
As our site will be enrolling about 75 patients in the trial, we are aiming to achieve the calculated statistical sample size by sharing our de-identified data results with the UCLA (University of California Los Angeles) Medical Center in California, conducting this same trial in the Los Angeles area with this same identical clinical study protocol. Our IND submission does cross-reference the UCLA IND already approved by the FDA.
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15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel will enter data from source documents corresponding to each subject into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a secure, de-identified, database. The study coordinators will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Sponsor/Investigator must make study data accessible to the monitor, IRB/ and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor/Investigator is required to maintain study records.

15.6 Monitoring

Monitoring visits will be conducted according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Sponsor/Investigator grants permission to the

appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation.

ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

15.8 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor/Investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

15.9 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.10 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, and HIPAA authorization and provide the documents to the IRB/. The consent form generated by the Investigator must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will include the IRB/ -approved copy of the Informed Consent Form in the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

15.11 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.12 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally, conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).

7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. EXAMPLE OF SCHEDULE OF STUDY SCHEDULE

	Day 1*	Days 3 and 7* if hospitalized	Day 30	Day 90
Informed Consent	X			
Medical History	X			X
Height	X			
Weight	X			
Vital Signs	X			
Troponin	X	X		
BNP	X	X		
C-Reactive Protein	X	X		
D-Dimer	X	X		
Echocardiogram	X			
WHO ORDINAL SCORE	X		X	X

* All labs can be obtained within ±1 day of the assigned time, baseline echocardiogram can be obtained within ±3 day of the assigned time.

APPENDIX 2. EXAMPLE OF SUBJECT DIARY

COLHEART-19 Study Subject Symptom and Drug Self-Administration Diary

Study Participant: _____

Instructions for Filling Out the Following Diary:

The study diary below is designed to keep track of your daily progress. Please include the date, the number of tablets of the study medication you took and check the corresponding dosage box for each day. Also, please indicate if you did not take a dose and a reason why. Please also list for us symptoms or side effects of the medication, and how overall you are feeling on the specified day. Please use the following scale:

1 = Overall very poor
2 = Poor
3 = Fair,
4 = Good, mild symptoms
5 = Excellent, no symptoms

Example Study Subject Entry:

Day/Date	Study Drug	Time/Dose Taken	Study Drugy		
Day 1 **Date:** 4/20/20	**Colchicine:** O 0.3 mg X 0.6 mg	Time: 09:00 X am O pm Dose Taken: X Full O Partial O ½ O ¼ O Missed Reason for Missing: _____	**Colchicine:** O 0.3 mg X 0.6 mg	Time: 08:00 O am X pm Dose Taken: X. Full O Partial O ½ O ¼ O Missed Reason for Missing: _____	Symptoms/Side Effects 1. Nausea 2. Shortness of breath 3. _____ 4. _____ 5. _____ Please rate overall how you are feeling today: Very Poor Fair Good Very Good 1 2 X 4 5

		Time:		Time:	Symptoms/Side Effects

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