BOSS-Covid-19 Study (BOSS-001)

Statistical Analysis Plan

TRIAL FULL TITLE	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of TQ Formula in Treating Participants who have Tested Positive for Novel Coronavirus 2019 (BOSS-Covid-19)
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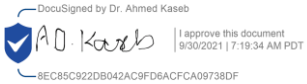

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1 Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FAS	Full Analysis Set

IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
LCVF	Last-Value-Carried-Forward
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDPO	Final Dataset for Primary Objectives
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption

NMAR	Not-Missing at Random
OHRP	Office for Human Research Protections
NMAR	Not-Missing at Random
PBMC	Peripheral Blood Mononuclear Cells
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

2 Introduction

2.1 Preface

In December of 2019, a series of acute atypical respiratory disease cases occurred in Wuhan, China which quickly spread to other areas. It was discovered that a distinctive coronavirus was responsible which was named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2, 2019-nCoV) as a result of its high similarity (~80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and high mortality in the years 2002–2003. This virus has resulted in a global pandemic with an increasing death toll. It is easily transmittable from human to human. The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan, China. It was later determined that human to human transmission played a major role in the subsequent outbreak. The disease caused by this virus was called Coronavirus disease 19 (COVID-19) and a pandemic was declared by the World Health Organization (WHO). COVID-19 has infected a large number of people worldwide, being reported in roughly 200 countries. The lack of a targeted therapy continues to be a problem.

There is currently no effective antiviral treatment for COVID-19. Existing drug alternatives as a result of clinical management of earlier discovered coronaviruses have been utilized in the treatment of COVID-19 patients.

The growing interest in phytomedicine brings along the issue of their safety, and the requirements to meet health standards. It has been shown that the seeds and oil of NS plant are characterized by a very low degree of toxicity. Black seed oil offers promising potential as a therapeutic option in management of SARS-CoV-2 as it has been shown in studies to possess beneficial properties like anti-viral effects.

The aim of this study is to provide a potential treatment for outpatients with a positive Covid-19 diagnosis, where the current standard of care (SOC) is limited to pain/symptom management such as acetaminophen. Any potential decrease in symptom longevity will benefit this population; and the potential benefits outweigh the minor risks in this case. In addition, this small, randomized phase II study will have a minimal number of patients exposed to the investigational product, and for a minimum duration.

2.2 Purpose

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting of BOSS-001 study, which is a randomized, double-blind, place-controlled study of Black Seed Oil in treating Covid-19 patient on an outpatient basis.

Also, exploratory analyses not necessarily identified in this SAP and/or specified in the corresponding protocol may be performed, should the investigating team and/or EC deem it necessary. Any post-hoc, or unplanned analyses not identified in this SAP will be clearly identified in the respective Clinical Study Report (CSR).

The following documents were reviewed and used as guiding references in preparation of this SAP:

- Clinical Research Protocol: BOSS-001 Version 6.0 dated 17 May 2021
- ICH E9: Statistical Principles for Clinical Trials (September 1998)
- E9 Statistical Principles for Clinical Trials Guidance document by FDA

Although we have quoted the relevant sections of the protocol in this SAP for convenience, the reader of this SAP is encouraged to also read the entire clinical protocol for details on the intervention and conduct of this study, and the operational aspects of clinical assessments and their timings subjects in this study.

3 Study Design

3.1 Overview

This is a randomized (1:1), double-blind, placebo-controlled phase 2 study to assess safety and efficacy of Total 3 g daily dose of Black Seed Oil ('TQ Formula ' this point forward) capsules versus placebo in treating patients who have tested positive for novel Coronavirus 2019 (Covid-19) in the outpatient setting.

Patients will be treated at a dose of 500 mg, 3 capsules, two times a day for 14 days from date of randomization.

Quantitative viral load as measured by RT-PCR will be evaluated at baseline and on days 7 and 14.

Covid-19 symptoms will be measured throughout the study using Modified FLU-PRO Plus.

3.2 Sample size

The total sample for this study is a minimum of 52 and up to 60 patients equally split between the placebo arm and the treatment arm.

The sample size is driven by the primary objective to compare the median time to sustained clinical response between the two arms.

For statistical analysis purposes, sustained clinical response is defined as a reduction to a score of </= 2 on all symptom scores on the Modified FLU-PRO Plus questionnaire and remaining </= 2 for

at least three days. Time to sustained clinical response will be calculated from the date of testing to the first day all symptoms are ≤ 2.

Power calculation will be based only on the first primary objective of the trial. Based on the median time to sustained clinical response reported by CDC [122], the expected median time to response in the placebo arm will be approximately 16 days from the onset of symptoms in outpatients. With a sample size of 20 in each arm, a difference in median time to sustained clinical response of 10 days between the intervention arm and the placebo arm will be able to be detected with 81.5% statistical power with 5% Type-1 error rate. Median time to sustained clinical response will be estimated based on 21-day follow-up. With an attrition expectation of around 20%, the planned accrual is 26 patients in each arm and potentially up to 30 patients.

3.3 Inclusion/Exclusion Criteria

3.3.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 and over, presenting with recent mild to moderate clinical symptoms of Covid-19 infection (per FDA guidance – see appendix 3)
4. Positive COVID-19 infection confirmed with a rapid antigen test at screening (or RT-PCR within the last 3 days) and confirmed with a RT-PCR test at baseline
5. A score of ≥3 on a minimum of 2 symptoms on the Modified FLU-PRO Plus
6. Ability to take oral medication and be willing to adhere to the dosing regimen (Twice a day – BID for 14 days)
7. For females of reproductive potential: negative pregnancy test at screening and use of highly effective contraception method during study participation and for an additional 4 weeks after the end of study drug administration
8. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner during study participation
9. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration

3.3.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Current or recent (within 4 weeks) treatment with any corticosteroids; however, high-dose inhaled steroids, which are used to treat acute or chronic bronchial inflammation, will be permitted
- Current or recent (within 4 weeks) treatment with any antivirals
- Room air oxygen saturation (SaO2) < 94% at screen
- Walking oximetry < 90% or participant unable to complete 6-minute walking oximetry test at screen
- Severe Covid-19 symptoms (severe per FDA classification – see appendix 3)
- Requires immediate admission to hospital for any reason
- Pregnancy or lactation
- Known allergic reactions to components of black seed oil, or thymoquinone
- Treatment with another investigational drug or other investigational intervention within 2 weeks of study start and throughout study duration.
- Significant hepatic disease (ALT/AST> 4 times the ULN); any laboratory parameter >/= 4 times the ULN
- History of moderate to severe CKD, (i.e. an estimated glomerular filtration rate less than 45 mL/min) at the time of enrollment or history of liver disease
- Patients with inflammatory bowel disease (such as Crohn's) that could affect the intestinal absorption of TQ Formula enteric coated capsules.
- Known HIV or Hepatitis C infection
- Influenza diagnosis (confirmed by testing) during screening or within prior 14 days
- Any uncontrolled condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation, as per investigator
- Current treatment with CYP2C9 substrates

3.4 Randomization, Blinding, and Patient Selection

Study participants will be randomized in a one to one fashion (1:1) using a block randomization with a block size of 4 independently within each center to receive either 3 g/day of TQ Formula (500 mg capsules x 3, BID) or placebo capsules (identical in appearance to active product) for 14

days. Participants will receive the full study supply (14-day medication) at randomization. Study capsules should be stored at ambient temperature (15°C to 25°C), away from direct sunlight. The study is double blinded; all subjects, investigators, and study personnel involved in the conduct of the study, including data management and primary biostatistician, will be blinded to treatment assignment. There will be an independent unblinded statistician. The unblinded study statistician will not otherwise participate in study procedures or data analysis.

A randomization list will be prepared by the unblinded statistician and provided to the investigational product (IP) depot for labelling. Sponsor and CRO study staff will remain blinded to study treatment. Randomization numbers will be assigned through the Electronic Data Capture (EDC) system.

Participants will complete a daily questionnaire on Covid-19 symptoms, which will be used to determine the primary endpoint for the study. For this reason, it is important that participants remain blinded to treatment allocation.

Unblinding

In the unlikely event that unblinding is required, the principal investigator can contact the unblinded statistician to unblind treatment. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding should be discussed in advance with the medical monitor if possible. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the participant's treatment assignment.

Final unblinding for the data analysis will not take place until and unless all data queries from data quality assessments are adequately addressed by each participating site.

3.5 Study Calendar and Data Collection

The schedule of the study visits and data to be collected are shown below.

Table 1. Schedule of events

Procedures	Day -3 to -1	Visit 1, Day 1	Day 4 +/-1 day	Day 7 +/- 1 day	Day 10 +/-1 day	Day 14 +/-1 day	Day 21 +/1 day	Day 45 +/- 1 day
Informed consent	X							
Demographics	X							
Medical history	X							

Inclusion/Exclusion Criteria Evaluation	X	X						
Rapid Antigen Test for Covid-19	X[c]							
RT-PCR sample for quantitative viral load analysis		X[c]		X		X		
Serum Collection (Blood sample for immune monitoring)		X		X		X		
Physical exam	X			X		X		
Vital signs	X	X		X		X		
Pulse Oximetry	X							
Walking Oximetry	X							

Procedures	Day -3 to -1	Visit 1, Day 1	Day 4 +/-1 day	Day 7 +/- 1 day	Day 10 +/-1 day	Day 14 +/-1 day	Day 21 +/1 day	Day 45 +/- 1 day
Height	X							
Weight	X							
Hematology	X		X[e]	X	X[e]	X		
Serum chemistry [a]	X		X[e]	X	X[e]	X		
Pregnancy test [b]	X							
Randomization		X						
Administer study intervention		X…..X						
Concomitant medication review	X	X	X	X	X	X	X	
Adverse event review/evaluation	X	X	X	X	X	X	X	X
Patient Reported Outcomes (Modified FLU-PRO Plus)*	X[+]	X……..X						
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	

a: Albumin, alkaline phosphatase, total bilirubin, direct bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium, CBC/diff, LDH, , CRP, prothrombin time, activated partial prothrombin time, , D-dimer b: Serum pregnancy test (women of childbearing potential).

c: Covid-19 Confirmatory test in addition to quantitative viral load d: Screening and Baseline can be combined

e: If clinically indicated at the discretion of the investigator

f: Visits at Day 4 (visit 2), Day 10 (visit 4), and Day 21 (final visit) will be telehealth and can be changed to in-person at the discretion of the investigator

g: In the event of a complete lockdown due to Covid, visits at Day 7(Visit 3) and Day 14 (Visit 5) could be replaced by home health visit for sample collection and telehealth visit for clinical evaluation.

*Administered everyday

+ Modified FLU-PRO Plus at Screen will be completed on site to determine if patient meets inclusion criterion

3.6 Primary Objective

Primary Objectives:

1. To evaluate if treatment with 3 g TQ Formula (500 mg per capsule, 3 capsules BID) given orally on outpatient basis can significantly reduce median time to sustained clinical response compared to placebo in participants with COVID-19 infection treated in the outpatient setting. Sustained clinical response is defined as a reduction of scores to </= 2 on all symptoms of the Modified FLU-PRO Plus and should be remaining </= 2 for at least three days.
2. To evaluate the safety and tolerability of TQ Formula (500 mg oral capsule, 3 capsules BID) when given to participants with COVID-19 infection

3.7 Secondary Objective

1. To compare the viral load profile over time (from baseline through to Day 14) between treatment with 3 g TQ Formula (500 mg per capsule, 3 capsules BID) given orally on outpatient basis and placebo in participants with COVID-19 infection treated in the outpatient setting
2. To compare the percentage of RT-PCR negative/undetectable (i.e., viral clearance) on Day 7 and Day 14 in participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) versus participants taking placebo
3. To compare the duration and severity of symptoms (measured by Modified FLU-PRO Plus) over time from Day 1 through Day 14 in total FLU-PRO Plus symptom severity score overall and in sub-domain scores (namely, Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal, Body/Systemic, Taste/Smell), between treatment with 3 g TQ Formula (500 mg per capsule, 3 capsules BID) given orally on outpatient basis and placebo in participants with COVID-19 infection
4. To investigate if there exists an association between viral load and symptom severity by study arm and if such associations change overtime.

Exploratory objectives:

1. To evaluate the basic pharmacokinetics of TQ Formula active ingredient (thymoquinone) at the same time points (Days 1, 7, and 14) in participants with COVID-19 infection.
2. To explore the effect of TQ Formula on inflammatory cytokines, coagulation factors and effector immune cells at same time points (Days 1, 7, and 14) in participants with COVID19 infection.

4 Study Endpoints

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint:

Measurement of the difference in median time to sustained clinical response in participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) versus participants taking placebo.

Sustained clinical response is defined as a reduction of scores to </= 2 on all symptoms of the Modified FLU-PRO Plus and sustained </= 2 for at least three days.

4.1.2 Secondary Efficacy Endpoints

1. Measurement of change in quantitative viral load from baseline, Day 7, and Day 14 using RT-PCR in participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) versus participants taking placebo with COVID-19 infection.
2. Percentage of negative/undetectable RT-PCR (i.e., viral clearance) on Day-7 and Day-14 in participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) versus participants taking placebo
3. Measurement of severity of, and change in, Covid-19 symptoms per total score as well as sub-scores (Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal, Body/Systemic, Taste/Smell) measured through Modified FLU-PRO Plus from Day 1 through Day 14 in participants with COVID-19 infection treated either with 3 g TQ Formula (500 mg per capsule, 3 capsules BID) or placebo.
4. Correlation Coefficient of quantitative viral load and symptom severity at baseline, at Day 7, and Day 14 in participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) versus participants taking placebo

4.1.3 Other Efficacy Endpoints

The endpoints for the exploratory aims are the following:

1. Measurement of thymoquinone and metabolites' concentration in the plasma on day 1, Day 7 and 14 using HPLC in patients treated with TQ Formula.
2. Measurement of the inflammatory cytokine production, coagulation factors and the various effector immune cell subsets in the Peripheral Blood Mononuclear Cells (PBMC) of all patients on Day 1, Day 7 and Day 14 using FACS.

If other analyses are needed beyond the endpoints mentioned above, this plan will be revised.

4.2 Safety Endpoints

Number of overall adverse events, related adverse reactions, and hospitalizations reported in participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) versus participants

taking placebo. All AEs/SAEs will be captured throughout the study as per schedule of assessments.

5 Statistical Methods

5.1 General Statistical Methods

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline and on study variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, range, and median). Frequency counts and percentage of subjects within each category will be provided for categorical data when appropriate in frequency and contingency tables.

5.2 Analysis Sets

The following are the main analysis datasets defined in the study protocol:

- Full Analysis Dataset: The Full Analysis Set (FAS) is defined as all randomized participants who receive at least one dose of study intervention.
- Final Dataset for Primary Objectives (FDPO): FDPO is defined as all randomized evaluable participants regardless of whether or not they received the assigned treatment regimen according to the evaluability definition above.
- Intent-to-treat (ITT) dataset: ITT dataset is defined as all randomized patients regardless of their adherence to or completion of the study regimen. This dataset includes all randomized participants even if they do not receive any dose or they withdraw from the study without completing the regimen or experience protocol violations.
- Safety Analysis Dataset: The Safety Analysis Set is defined as participants who take at least one dose of study intervention.
- Per-Protocol Analysis Dataset: The Per-Protocol Analysis Set (PP) is defined as all participants in the FAS who complete all visits up to and including Day 14, are compliant with study medication and do not have any major protocol violation. Major protocol violations will be identified prior to breaking the blind.

5.3 Statistical Analyses

5.3.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized with descriptive statistics. Continuous variables will be summarized with n, mean, standard deviation, minimum, maximum and median. Frequency counts and percentage of subjects within each category will be provided for categorical data.

5.3.2 Primary Analyses

Primary estimand-1 is defined to be the difference of median time to sustained clinical response between participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) and participants taking placebo regardless of whether or not they actually receive their assigned therapy (ITT) and assuming that their hospitalization and treatment discontinuation rates will be similar. Possible intercurrent events for this estimand can be, though expected to be quite rare, hospitalization (i.e., transitioning from outpatient status to inpatient status) and treatment discontinuation, both of which may lead to potential missing data or change in the primary measures. The study participants will be reminded to submit their Modified FLU-PRO Plus questionnaires even after these intercurrent events to avoid missing data as much as practically possible. Hospitalization-free, while-on-study and per-protocol treatment versions of the above estimand will also be considered within each population definitions above.

Median time to sustained clinical response for the treatment and placebo arms will be estimated using the Kaplan-Meier method and Log-rank test will be utilized to compare the time to sustained clinical response distributions between the two study arms using LIFETEST procedure in SAS Version 9.4 ® (SAS Institute, Cary, North Carolina, USA). Events will be defined as cases that attain sustained clinical response while on study and time to event will be calculated as the days from the date of symptoms onset to the date that all symptoms are below Level-2 (‘A little bit’) on the Modified FLU-PRO Plus questionnaire. Patients who do not attain to clinical response while on study will be censored on Day-21 or on the day they are off study before Day-21 due to other reasons.

Although all analyses will be conducted based on the intent-to-treat principle, sensitivity analyses based on the adherence to the protocol regimen will also be carried out for the primary as well as secondary objectives. Sensitivity analyses will also include hospitalization-free, while-on-study, and per-protocol treatment cohorts as described above.

Primary Estimand-2 for the safety objective is the difference of frequencies of Adverse Events and Serious Adverse Events between participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) and participants taking placebo regardless of whether or not they actually receive their assigned therapy (ITT) and assuming that their hospitalization and treatment discontinuation rates will be similar. The above mentioned intercurrent events are also applicable for this safety estimand. Therefore, hospitalization-free, while-on-study and per-protocol treatment versions of the above estimand will also be considered within each population definitions above.

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5.3.3 Secondary Analyses

Analysis plan for Secondary Aim-1:

Secondary estimand-1 is defined to be the slope difference of viral load change overtime between participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) and participants taking placebo regardless of whether or not they actually receive their assigned therapy (ITT) and assuming that their hospitalization and treatment discontinuation rates will be similar.

The first secondary endpoint of this clinical trial is the differential change of viral load distribution overtime between the two-study arm. As the viral load will be measured at Baseline, on Day-7, and on Day-14 (and potentially for some patients in Day-4 and Day-10 visits), the outcome variable of interest will be a longitudinal interval-scale measure. To assess the differential behaviour of viral load overtime between the two study arms, Random Coefficients Models will be utilized where viral load will be the dependent variable and study arm and time will be main predictors. Viral load measures may be subjected to some data transformation (e.g., log transformation) to improve the model fit and assumptions as necessitated by model diagnostics. In addressing this objective, all available data will be utilized; that is, in addition to the evaluable patients, data from non-evaluable patients such as data only at baseline visit or data at baseline and Day-10 for example will be used to improve the local fit of the underlying model. To assess differential behavior in total symptom severity score, time*study-arm interaction will be investigated as well. The above mentioned intercurrent events, namely, hospitalization (i.e., transitioning from outpatient status to inpatient status) and treatment discontinuation, are applicable for Secondary estimand-1 as well. Therefore, hospitalization-free, while-on-study and per-protocol treatment versions of the above estimand will also be considered within each population definitions above, namely, Full Analysis Dataset (FAS), Final Dataset for Primary Objectives (FDPO), and Per-Protocol Analysis Dataset (PPAS). The above analysis will be carried out using the MIXED procedure of SAS software.

Analysis plan for Secondary Aim-2:

Secondary estimand-2 is defined to be the proportion difference of patients with RT-PCR negative/undetectable viral loads between participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) and participants taking placebo regardless of whether or not they actually receive their assigned therapy (ITT) and assuming that their hospitalization and treatment discontinuation rates will be similar. To address this estimand, the percentages of RT-PCR negative/undetectable viral loads between the two study arms will be estimated and compared using Fisher's Exact test at Day-7 and Day-14 visits. The above mentioned intercurrent events for

the primary endpoint are applicable for Secondary estimand-1 as well. Therefore, hospitalizationfree, while-on-study and per-protocol treatment versions of the above estimand will also be considered within each population definitions above. Beyond the single test of independence at each time point, Logistic Regression models will also be constructed to investigate the interaction of the study arms with other factors if interest such as gender, age, etc.

Analysis plan for Secondary Aim-3:

Secondary estimand-3 is defined to be the difference of total and subdomain symptom scores measured through Modified FLU-PRO Plus questionnaire between participants taking 3 g TQ Formula (500 mg per capsule, 3 capsules BID) and participants taking placebo regardless of whether or not they actually receive their assigned therapy (ITT) and assuming that their hospitalization and treatment discontinuation rates will be similar. To address this estimand, the differential change of total and subdomain symptom severity score measured by Modified FLUPRO Plus overtime between the two-study arm will be estimated and compared between the two study arms. As the total and subdomain symptom severity score will be measured at Baseline (Day-1) and on each day through Day-14, the outcome variables of interest will be a longitudinal interval-scale measures. To assess the differential behaviour of total and subdomain symptom scores overtime between the two study arms, Random Coefficients Models will be utilized where total and each of the subdomain symptom severity score will be the dependent variables and study arm and time will be main predictors. Total and subdomain symptom severity scores may be subjected to some data transformation (e.g., log transformation) to improve the model fit and assumptions as necessitated by model diagnostics. In addressing this objective, all available data will be utilized; that is, in addition to the evaluable patients, data from non-evaluable patients such as data only at baseline visit or data just at baseline and Day-10 for example will be used to improve the local fit of the underlying model. To assess differential behavior in total symptom severity score, time*study-arm interaction will be investigated as well. When scientifically indicated, aggregated symptom severity scores may be defined through combining a set of subdomains such as Nose, Eyes. And Throat. The above mentioned intercurrent events are applicable for Secondary estimand-1 as well. Therefore, hospitalization-free, while-on-study and per-protocol treatment versions of the above estimand will also be considered within each population definitions above. For the above analyses, the MIXED procedure of SAS software will be utilized.

Analysis plan for Secondary Aim-4:

Secondary estimand-4 is defined to be the assessment of whether or not a significant correlation between quantitative viral load and symptom severity exists and if so, whether or not such a linear association is dependent on the study arm. To address this estimand, the association between quantitative viral load and symptom severity will be investigated through linear regression models using the GLM procedure of SAS software, where total symptom severity score will be the dependent variable predicted by the quantitative viral load measures in the model at each visit. Study-Arm*viral load interaction will be added to the model to investigate if any association between viral load and symptom severity is mitigated by the study treatment. The above mentioned intercurrent events are applicable for Secondary estimand-1 as well. Therefore, hospitalization-free, while-on-study and per-protocol treatment versions of the above estimand will also be considered within each population definitions above.

5.3.4 Other Analyses

Analysis plan for Exploratory Aim-1:

Descriptive and graphical statistics will be used to present the distribution of metabolites' concentration markers in the plasma on day 1, Day 7 and 14 using HPLC within each study arm. These markers will also be compared for differential distribution between the arms using Wilcoxon-Mann-Whitney test at each visit. To compare the change over time in these markers, Random Coefficients Models will be utilized where each of these markers will be the dependent variable and study arm and time will be main predictors.

Analysis plan for Exploratory Aim-2:

Descriptive and graphical statistics will be used to present the distribution of the inflammatory cytokine production, coagulation factors and the various effector immune cell subsets in the Peripheral Blood Mononuclear Cells (PBMC) of all patients on Day 1, Day 7 and Day 14 using FACS within each study arm. These markers will also be compared for differential distribution between the arms using Wilcoxon-Mann-Whitney test. Like above, to compare the change over time in these markers, Random Coefficients Models will be utilized where each of these markers will be the dependent variable and study arm and time will be main predictors.

In addition to the primary analysis described in Section 5.3.2 above, Response Free Survival (RFS) distributions will be compared using Cox-Proportional Hazards Models between the two

study arms controlling for other factors of interest such as gender, baseline viral load, age etc. The interaction of the study arm with these covariates will be also investigated. Considering the small size of the study, number of covariates to be added to such multivariable models will be limited. We expect that only 2-3 covariates will be added to these models in addition to the study arm.

5.3.5 Covariate and Subgroup Analyses

Covariate and subgroup analyses will be presented when applicable and supported by the available data, considering that the sample size of each study arm is already limited by up to 30 subjects per arm.

5.3.6 Safety Analyses

Safety will be evaluated by summary of adverse events. Adverse event incidence rates will be summarized for each study arm, namely, Active Drug and Placebo Arms, in terms of severity and its relationship to study drug. A tabulation of Serious Adverse Events (SAEs) will be provided within each study arm with the number of patients experiencing a given AE or ADE, and the number of episodes while on study. Similar reports will be generated for AE monitoring purposes for the entire study cohort without unblinding of the study participants while the study is still ongoing.

6 Definitions for Clinical Evaluations

6.1 Follow-Up Time Points

The treatment time for each participant is 14 days and the follow-up time is for 7 days or until ongoing adverse events are resolved up to 45 days as part of safety follow-up.

6.2 Points of Enrollment

Subjects will be considered enrolled in the study when they have been informed of all aspects of the study, had ample time to review the Informed Consent document, signed the Informed Consent document, satisfied the Inclusion/Exclusion Criteria, and randomized.

6.3 Definitions for Clinical Evaluation

Clinical evaluation will be done using Flu-Pro Plus questionnaire modified for Covid-19 patients treated in an outpatient setting. The participants will fill out the questionnaire at the time of Screening, Enrollment, and from Day-1 to Day-21 post randomization each day using online data capture forms.

7 General Considerations

If a subject is not able to complete the study after being enrolled, the Investigator, or designee will document the last contact with the subject. All attempts to contact the subject will be documented in the source documentation. Missed or out-of-range visits will be considered protocol deviations.

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7.1 Missing Data and Outliers:

In this study, the primary objective is driven by data collected during the baseline visit and up to Day-21; considering the short treatment and follow-up time, missing data is expected to be minimal. We do not anticipate excessive missing values; however, missingness structure will still be analyzed as to whether or not the missingness is Missing Completely at Random (MCAR), or Missing at Random (MAR), or Not-Missing at Random (NMAR). In the event of MCAR and MAR, sensitivity analyses will be carried out by using Multiple Imputation (MI) techniques when appropriate. Specifically for the Modified FLU-PRO Plus data, Last-Value-Carried-Forward (LVCF) imputation approach will be utilized as this assessment will be for Day-1 through Day-21 and LVCF approach would be appropriate to impute intermittent missing values in these time series type data.

The data quality checks will be an ongoing effort for the study and potential outliers will be detected and resolved as much as possible while the study is ongoing. In the analysis phase, the outliers will be evaluated based on whether or not they are influential values in given statistical model a given outlier may be perfectly in line with the model built and does not necessarily mean problematic for modeling assumptions. If they are found to be influential, then possible data transformation approaches such as log-transformation will be considered.

7.2 Protocol Violations and Deviations

Missed visits and out of range visits will be considered protocol deviations while such participants will still be deemed evaluable for the primary objective. Investigators will not deviate from the clinical protocol except to deliver emergency care or to eliminate an immediate hazard to the subject. All study deviations from the clinical protocol will be captured in the study CTMS database. All deviations with the potential to affect subject safety, rights, or well-being will also be reported as required by the IRB/EC and to sponsor.

7.3 Disposition of Subjects and Withdrawals

All subjects who provide informed consent and are enrolled will be accounted for in this study. Subjects maintain the right to discontinue their participation in the study at any point. If a subject

exercises this right, the Investigator will make every effort to ascertain and document the reason for withdrawal.

7.4 Sensitivity Analysis

Sensitivity analysis is not applicable for this study.

7.5 Changes to Planned Analysis after Blind Review of Data and Unblinding Consideration (if Applicable)

Not applicable.

7.6 Interim Analysis and Data Monitoring

There is no planned interim analysis for the primary objective of the study; however, there will be safety interim analyses after the initial cohort of 12 patients have been enrolled and have received at least one dose of the assigned drug. This safety interim analysis will be conducted without unblinding the patients. As part of this safety interim analysis, if two or less number of patients in this initial cohort of 12 patients experience Grade 3+ adverse events attributable to the study regimen and not resolved through symptomatic treatments within 48 hours, there will be no need for unblinding the safety cohort; however, if there are 3 or more cases with Grade 3+ adverse events attributable to the study regimen and not resolved through symptomatic treatments within 48 hours, the enrollment will be halted, this initial cohort of patients will be unblinded to evaluate the distribution of the AEs between the placebo and the study drug, and the possible corrective amendments will be considered.

7.7 Timing with Respect to Database Locking

The data quality checks will be an ongoing effort while the study is still on. When all patients are enrolled and complete their modified Flu-Pro Plus assessment to Day 21, a complete dataextraction will be requested for an efficacy data quality control. Once the efficacy data is deemed to be complete and accurate, the efficacy data will be locked and another complete data extraction will be requested to generate a preliminary efficacy report. As part of this preliminary efficacy analysis, the study statistician will be unblinded but all other member of the study team will remain blinded and the preliminary safety report will not contain any individual level data. Upon the completion of the 45-day safety follow-up of the last enrolled patient,, there will be a final data quality assessment finalizing the safety parameters, generating final set of queries for the study sites to correct/modify/update. Once all data quality check queries are adequately addressed, the study database will be ordered to be locked and the entire study team will be unblinded to patient randomization.

7.8 Analysis Software

All analysis will be performed using SAS® Software version 9.4 or later. When appropriate, Rpackage will be used as well.

7.9 List of Tables, Figures and Listings

Demographic characteristics table, AE and SAE tables, tables of Covid-19 test results both from the rapid test and RT-PCR, the distribution statistics table for the viral load assessments, any other secondary objective measure tables. Modified FLU-PRO Plus assessments will be shown graphically as time series plot with a reference line at Level-2 (‘Somewhat’) where the y-axis will show the scale from ‘Not at all (Level-0)’ to ‘Very much (Level-4)’.

8 References

8.1 Applicable Regulatory Guidelines:

- ICH E9: Statistical Principles for Clinical Trials (September 1998)

8.2 Other applicable Documents

Not Applicable