Statistical Analysis Plan

Multicenter, adaptive, randomized, placebo-controlled, double blind, parallel-group Phase 2/3 trial, to study efficacy and safety of two doses of raloxifene in adult paucisymptomatic COVID-19 patients.

Statistical Analysis Plan: Version (Final 1.0), Date: 07 Jul 2021

Protocol Number: Version No. 3.0 – FINAL, Date: 22 Dec 2020

Name of the Drug: Raloxifene (RLX)

Sponsor Company: Dompé farmaceutici s.p.a. [Dompé]
Via Santa Lucia 6; 20122 Milan, Italy

Confidentiality Statement

Confidentiality Notice: This document contains confidential or legally privileged information that is intended only for the use of Agati Clinical Informatics. You are hereby notified that any disclosure, copying, or distribution of the contents of this document is strictly prohibited.

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
BT	Body Temperature
CI	Confidence Interval
CP	Conditional Power
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DB	Data Base
ENR	Enrolled Analysis Set
EOS	End of Study
ETDV	Early Trial Discontinuation Visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IP/IMP	Investigational Product/ Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NEWS	National Early Warning Score
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PI	Principal Investigator
PP	Per Protocol
PR	Pulse Rate
PT	Preferred Term
QC	Quality Control
RTF	Rich Text Format
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SpO2	Oxygen Saturation
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TLF	Tables Listings Figures
WHODD	World Health Organization Drug Dictionary

2 INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol RLX0120. It describes the data to be derived, summarized and the statistical analyses to be performed.

This Statistical Analysis Plan (SAP) is based on study protocol version 3.0, dated 22 Dec 2020.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy and safety of two different doses of raloxifene orally administered compared to placebo in patients with early diagnosis of paucisymptomatic COVID-19

3.1.1 PRIMARY OBJECTIVES

- Evaluation of the effectiveness of therapy in reducing the proportion of patients who still have viruses in the upper airways after 7 days of therapy.
- Evaluation of the effectiveness of therapy in reducing the proportion of patients who requires supplemental oxygen therapy and/or mechanical ventilation within 14 days of starting therapy.

3.1.2 SECONDARY OBJECTIVES

- Evaluation of the effectiveness of therapy in reducing the proportion of patients who still have viruses in the upper airways after 14 and 28 days of therapy.
- Evaluation of the effectiveness of therapy in reducing the proportion of patients who requires supplemental oxygen therapy and/or mechanical ventilation within 7 or 28 days of starting therapy.
- 7, 14 and 28 days drug safety and tolerability profile.
- Assessment of body temperature, blood and biochemical parameters between T0 and T28.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINTS

- Virologic outcome - Proportion of patients with undetectable SARS-CoV-2 at PCR at day 7 after randomization.
- Clinical outcome - Proportion of patients who does not require supplemental oxygen therapy (NEWS ≤2) and/or mechanical ventilation at day 14 after randomization.

3.2.2 SECONDARY ENDPOINTS

- Proportion of patients with undetectable SARS-CoV-2 at PCR at day 14 after randomization at day 28 after randomization.
- Proportion of patients who does not require supplemental oxygen therapy

(NEWS ≤2) and/or mechanical ventilation at day 7 and 28 after randomization.

- Proportion of patients in each NEWS category at time 7, 14 and 28 after randomization.
- Mean value of NEWS category at time 7,14 and 28 after randomization.
- Proportion of patients with any adverse event with grade ≤ 2 according to CTCAE at day 7, 14 and 28 after randomization.
- Proportion of patients with any severe adverse events (grade ≥ 3 according to CTCAE) at day 7, 14 and 28 after randomization.
- Proportion of hospitalized patients who at the beginning of the study were at domicile isolation at day 7, 14 and 28 after randomization.
- Proportion of patients admitted to intensive care at day 7, 14 and 28 after randomization.
- Proportion of survivors at day 7, 14 and 28 after randomization.
- Mean variation of value of the following biomarker parameters, from baseline to day 7, 14, 21 and 28 after randomization:
  - Complete blood cell counts.
  - Hepatic function (ALT, AST and bilirubin).
  - Coagulation (PT, aPTT and INR).
  - Other marker including (D-dimer, CPK, LDH).
- Quality of life questionnaire 3 months after the randomization.

4 STUDY DESIGN AND SCHEDULE OF EVENTS

4.1 STUDY DESIGN

4.1.1 DESCRIPTION OF THE STUDY

This is a Multicenter, adaptive, double blind, randomized, placebo controlled, parallel group, to study efficacy and safety, with the following adaptive components:

- Parallel multi-arms (2 interventional arms and 1 placebo control arm).
- A 2-stage sequential design (1 interim analysis + 1 final analysis).
- Sample size re-calculation at interim stage.
- Stopping rule for efficacy or futility at interim stage.

4.1.2 SAMPLE SIZE

The sample size of the study has been based on the following assumptions:

- Virologic assumption: Early treatment with antivirals increases the proportion of patients with undetectable SARS-CoV-2 in upper respiratory tract at day 7 after therapy from 25% to 50%.
- Clinical assumption: Early treatment with antivirals increases the proportion of

patients who recover without need of mechanical ventilation and/or supplemental oxygen therapy by the day 14 after therapy from 50% to 75%.

Based on these assumptions and considering a randomization ratio 1:1:1, the sample size will be adaptively determined to achieve a power greater than 80% to show superiority of raloxifene vs placebo in terms of either one of primary endpoint and controlling the one-sided alpha below 0.025.

Sample size will be determined through the following steps:

- an interim analysis will take place when 50 patients per arm (N=150) have reached their primary endpoints (i.e. assessments available).
    - In case of efficacy of at least one treatment arm or futility of both arms (see criteria in protocol section 9.3) the study enrollment will be stopped,
    - otherwise the actual number of new patients in each arm may be blindly reassessed according to observed efficacy of the best favourable and promising arm;
- in case of continuation of the study to the final stage, it is expected to randomize on average additional 174 patients, depending on sample size reassessment and possible dropping of an ineffective treatment arm. Expected sample size will be between 250 and 450 randomized patients;
- drop-outs of randomized subjects will not be replaced.

This approach allows either to minimize the number of enrolled patients if the experimental assumptions are too conservative or to have a good power level if they are too optimistic.

Pocock's spending functions and conditional power (CP) will be used to control the type I and II errors, considering that interim analysis will be performed when half of the initial planned patients have been reached the primary endpoints (i.e. assessments available).

Bonferroni method is used to adjust for multiple endpoint vs treatment comparisons. Sample size calculation has been performed through simulation (100000 replications). The statistical software used for simulation was SAS®, Version 9.4.

4.1.3 DESCRIPTION OF TREATMENTS

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene (60 mg Group 1, 120 mg Group 2 – treatment groups) or placebo (Group 3 - control group) will be taken on by the patients for two weeks.

The patients will be randomly (1:1:1) assigned to receive either raloxifene treatment or placebo:

- Treatment groups:
    - Group 1: will receive one capsule of raloxifene 60 mg and one capsule of placebo.

- Group 2: will receive two capsules of raloxifene 60 mg.

- Control group:
  - Group 3: will receive two capsules of placebo.

4.1.4 DESCRIPTION OF THE STUDY FLOW

This study will be performed in clinical centers located in Europe. At each study center, the Principal Investigator (PI) will be responsible for ensuring that the investigation is conducted according to the signed Investigator agreement, the protocol, GCP guidelines, and local regulations.

Screening investigations on patient will be done only after signing of informed consent.

At the end of the screening period, patients meeting the entry criteria for this study will be randomized (1:1:1) to 1 of 3 treatment groups (group 1, group 2 or group 3) and instructed by a physician on the correct self-administration of the treatment and completion of the patient diaries.

The study will be a total of 5 weeks in duration:

Screening Period	10 days
Treatment Period	2 weeks (14 days)
Follow-up Period	2 weeks (14 days)

A quality of life questionnaire will be submitted at 3 months after the randomization.

4.1.5 SCHEDULE OF ASSESMENTS

Assessment of efficacy and safety will be done periodically during the study as given in the schedule of assessment table in protocol section 2.

4.2 PLANNED ANALYSES

Statistical analysis and reporting will be performed by Agati Clinical Informatics, India for this study.

SAS source (raw) data will be transferred as SAS dataset (.sas7bdat), together with laboratory reference range, and any support datasets. Transfer will occur via secured EXOM Group Share Point Portal with limited and restricted access.

The statistical analysis will be based on validated analysis datasets prepared by Agati Clinical Informatics, India.

Production SAS programmers will create derived datasets from the Source (Raw) datasets as per the mapping instructions given in the analysis mapping specifications. Simultaneously, the Validation (QC) SAS programmer will create the same derived datasets independently and will do a comparison with production datasets to validate them.

Validated draft derived datasets will be sent to the Study Lead Biostatistician for review and approval. When the final source data transfer is made available (after database lock), the production and validation programs will be re-run to create the final derived datasets deliverable to be used for the final statistical analysis.

The statistical SAS output generated after running SAS programs will be copied in a Word file and paginated as specified in the Section 18 of this SAP.

Tables, Listings and Figures will be presented according to TFL Shells document created and finalized based on approved version of the SAP.

4.3 INTERIM ANALYSIS

An interim analysis was planned for this study when half (i.e 50 participants per arm (N=150)) of the planned evaluable patients would have reached the primary endpoints at 7 and 14 days (i.e., assessments available).

The intent of the interim analysis was either for identification of early superiority of raloxifene (early efficacy), or for an early stop of one or both treatment arms for futility, or for blind sample size reassessment.

Due to the premature interruption of the enrolment (with 68 patients included in the study), no interim analysis will be done.

4.4 OVERALL ANALYSIS

Final analyses identified in this SAP will be performed by Agati Clinical Informatics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Population and Unblinding of Study Treatment.

For primary and secondary efficacy endpoints, p-value, lower and upper 95% Confidence Limits (CL) will be also presented based on the statistical analysis performed.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max).

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per variable of interest will be the default summary presentation, if appropriate and wherever required the number of missing values will be presented as a “Missing” category. If appropriate, 95% confidence intervals around the percentage will be presented.

Time-to-event endpoints will be assessed by the Kaplan-Meier (K-M) method. Time to event curves will be compared (i.e comparisons of each active treatment group versus placebo) using log-rank test and estimates of hazard ratio will be obtained using Cox proportional hazards model after performing diagnostics of proportional hazard assumption (investigated with a time dependent exploratory variable treatment*{log[time to event]}; if the p-value from the Wald Chi-squared statistic for this variable is less than 5% there is evidence of a departure from the adjusted model assumptions.). K-M estimates of median survival time associated with each treatment group will be provided along with 25th and 75th percentiles and their 2-sided 95% CIs (based on Greenwood’s method). K-M estimates will be presented at Day 7, 14 and 28 for each treatment group. K-M curves will be plotted comparing treatment groups with the number of patient-at-risk in each treatment group at exact time points. Patients who are ongoing and who are free from event at the time of DB lock will be censored at the DB lock date. Patients who have discontinued without an event will be censored at the date of discontinuation. Patients who are died will be considered as censored with death

date as date of censored.

5 ANALYSES POPULATION

Agreement and authorization of patients included/excluded from each analysis Population will be performed on a case-by-case basis before the database lock/un-blinding.

5.1 ALL PATIENTS ENROLLED [ENR]

The Enrolled (ENR) population will contain all patients who provided informed consent for this study.

The Enrolled (ENR) population will be used for the Patient disposition Table and Listings. And it will be analysed according to the randomized treatment, if applicable.

5.2 RANDOMIZED POPULATION [RND]

The Randomized (RND) population will contain all patients in the ENR Population who were randomized to the study, regardless of whether they received study medication or not. Patients will be analysed according to the treatment they were randomized.

5.3 FULL ANALYSIS SET [FAS]

The Full Analysis Set (FAS) population will consist of all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo).

The Full Analysis Set (FAS) population will be used for Primary and secondary efficacy analyses, all the demographics and baseline characteristics Tables and Figures. Patients will be analysed according to the treatment they were randomized.

5.4 SAFETY POPULATION [SAF]

The Safety (SAF) population will consist of all randomized patients who received at least one dose of the study medication.

The Safety (SAF) population will be used to present results on safety data. Safety data will be analysed according to the treatment which patients have received.

5.5 PER PROTOCOL POPULATION [PP]

The Per Protocol (PP) population will consist of all randomized patients who received at least one dose of the study medication and do not have any Major Protocol Deviations.

The Per Protocol (PP) population will be used for sensitivity analyses of the efficacy endpoints. Patients will be analysed according to the treatment they were randomized.

6 PROTOCOL DEVIATIONS

All the protocol deviations will be discussed on a case by case basis by the clinical team prior to database lock. Any significant deviation from the protocol will be

reviewed and a decision taken regarding evaluation for each analysis population.

7 GENERAL CONSIDERATIONS

7.1 REFERENCE START DATE AND STUDY DAY

In general, reference start date is defined as the day of the first dose of study medication (Study Day 1: first day) and will appear in every listing where an assessment date or event date appears.

Study Day will be calculated from the reference start date and will be used to show start / stop day of assessments and events.

If the date of the assessment/event is on or after the reference start date, then:

Study Day = (date of assessment/event – reference start date) + 1

If the date of the assessment/event is prior to the reference start date, then:

Study Day = (date of assessment/event – reference start date)

In the situation where the assessment/event date is partial or missing, the date will appear partial or missing in the listings, and Study Day and any corresponding duration will be presented based on the imputations specified in Appendix 2 (Partial Date Conventions).

7.2 STUDY BASELINE AND POST BASELINE

7.2.1 BASELINE

Unless otherwise specified, study baseline is defined as the last non-missing measurement taken prior to first IMP administration.

7.2.2 POST-BASELINE

Post-Baseline is defined as the measurement taken after the first IMP administration.

7.2.3 CHANGE FROM BASELINE

For some quantitative measurements, change from baseline will be calculated as:

Change from baseline = Value at Post-Baseline Visit – Baseline Value

7.3 EARLY WITHDRAWAL FROM THERAPY OR ASSESSMENT AND END OF STUDY

7.3.1 EARLY TRIAL DISCONTINUATION VISIT AND UNSCHEDULED VISITS

In general, for by-visit summaries, data recorded at the nominal visit will be presented.

Unscheduled measurements will not be included in by-visit summaries. Listings will include scheduled, unscheduled, and early trial discontinuation visit (ETDV).

7.3.2 PREMATURE DISCONTINUATION

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study protocol procedures. Patients can be prematurely discontinued from the study for one of the following reasons:

Primary Reason for treatment discontinuation:

- Failure to meet inclusion/exclusion criteria or severe protocol violations
- Negative Nasopharyngeal swab
- Withdrawal of consent
- Lost to follow-up
- Study terminated by the Sponsor
- Documented disease progression
- Development of AE or unacceptable toxicity, precluding further therapy with the study drug
- Pregnancy
- Hypoalbuminemia at a level considered clinically relevant by the investigator
- Other reasons

Primary Reason for study discontinuation:

- Failure to meet inclusion/exclusion criteria or severe protocol violations
- Withdrawal of consent
- Lost to follow-up (Every effort must be made to contact the patient; a registered letter must be sent)
- Study terminated by the Sponsor
- Development of AE or unacceptable toxicity, precluding further therapy with the study drug
- Pregnancy
- Other reasons

In case of discontinuation, patients will undergo a remote Early Trial Discontinuation Visit aimed to assess physical abnormalities, vital signs and transdermal oxygen saturation measurement.

7.3.3 END OF STUDY (EOS)

The EOS is defined as the last day the last patient completes the last study assessment, or retracts the consent to participate in the study, or withdraws from the study, or is deceased or otherwise lost to follow-up.

7.4 ALL LISTINGS

All data will be listed by the patient.

7.5 SOFTWARE VERSION

All statistical analyses will be conducted using the SAS® System version 9.1.3 or higher.

8 STATISTICAL METHODOLOGY AND CONSIDERATIONS

8.1 ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

In the analysis of primary endpoints and secondary endpoints, the following factors/covariates will be considered in the Binary Logistic regression and Repeated Measures Logistic regression model as described in the SAP section 14.1

- Treatment group;
- Center;
- Age group;
- Status (Male, Female pre-menopausal status, Female post-menopausal status);
- For Clinical outcome: Baseline NEWS value.

8.2 MULTICENTRE STUDIES

This study will be conducted by multiple investigators at multiple centres and randomization will be stratified by site and gender. Both stratification factors will be included in the primary efficacy analysis model.

8.3 SENSITIVITY AND SUPPORTIVE ANALYSES

The virologic and clinical primary efficacy endpoints will be analysed using the same Binary Logistic regression procedure given in SAP section 14.1.1 on PP Population using observed data only; these analyses will be performed to explore the robustness of the primary results versus protocol adherence.

8.4 MULTIPLE COMPARISONS/ MULTIPLICITY

Bonferroni method is used to adjust for multiple endpoints and treatment comparisons.

8.5 EXAMINATION OF SUBGROUPS

Statistical tests for interaction (between subgroup and treatment arm) will be performed to decide about the need to further investigate subgroups of the trial population based on the following variables:

- age group (< median vs ≥ median, where median is calculated based on ENR population)
- gender (Male vs Female)
- Status (Male, Female pre-menopausal status, Female post-menopausal status);

Subgroup analysis will be performed if interaction effects are statistically significant at 0.15 level of significance.

Subgroup analysis will be performed for the primary efficacy endpoints. Descriptive and appropriate inferential statistical tests will be used. All subgroups will be analysed using FAS population.

9 OUTPUT PRESENTATIONS

SAP Section 17 and Appendix 1 includes conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations shell for this study and therefore the format and content of the summary tables, figures and listings to be provided.

The reference analysis population of each table and line listing will be reported in the corresponding table, listing and figures.

10 PATIENT DISPOSITION, WITHDRAWALS AND PROTOCOL DEVIATIONS

A detailed description of the patient disposition will be provided. The number of patients screened, screen failures, randomized, randomized but not dosed, completed, as well as the number of dropouts, with reasons for treatment discontinuation, study discontinuation and major protocol deviations. The summary of analysis populations, a summary of reasons for exclusion from analysis populations will be presented.

Patient disposition details will be presented in listing.

Furthermore, Summary of Protocol Deviations table and an individual data listing of protocol deviations will be produced.

The Enrolled (ENR) population will be considered for this analysis. And data will be summarized by randomized treatment group.

11 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Summary of demographic data and other baseline characteristics will be tabulated for the Full analysis set (FAS) population and will be summarized by randomized treatment group.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and baseline characteristics will be reported by treatment for this study:

- Demographic variables:
  - Age (years)
  - Sex (Male, Female)
  - Race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other pacific islander, NA, Other)
  - Height (cm)
  - Weight (Kg)

  - BMI
  - Smoking habits
  - Status (Male, Female pre-menopausal status and Female post-menopausal status)
- Female Patient childbearing potential (Yes/No)

Default frequency tabulations will be provided for categorical variables and descriptive statistics will be provided for quantitative parameters.

11.1 MEDICAL HISTORY

Medical history information will be tabulated for both FAS and SAF analysis populations and will be summarized accordingly (see SAP section 5).

All verbatim terms will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to MedDRA dictionary September 2020, version 23.1

Medical conditions which are not ongoing at Screening visit will be considered as previous diseases while those reported as “ongoing” in CRF will be considered as concomitant diseases.

Medical History of special interest as per collected in CRF will be listed for ENR population.

12 PRIOR AND CONCOMITANT MEDICATIONS

All medications taken by the patients during the Screening will be recorded by the Investigator in the CRF.

Prior and concomitant medications will be tabulated for both the FAS and SAF analysis populations and will be summarized accordingly. Prior and concomitant medications will be coded using WHODD Global September2020 version.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e., concomitant.

Prior medications are those which stopped prior to the date of first study medication administration.

Concomitant medications are those which

- started prior to, on or after the date of first study medication administration and started no later than end date of the study, and
- ended on or after the date of first study medication administration or were ongoing at the end of the study.

The following tables will be presented:

- A frequency tables of prior medications by primary therapeutic subgroup (ATC level subgroup) and generic name.
- A frequency tables of concomitant medications by primary therapeutic subgroup (ATC level subgroup) and generic name.

Listing of prior/concomitant medication will be provided.

13 STUDY MEDICATION EXPOSURE AND COMPLIANCE

13.1 DURATION OF EXPOSURE AND TREATMENT COMPLIANCE

Data will be summarized by actual treatment groups for Safety (SAF) population with descriptive statistics.

Total duration of study medication exposure considered in days and will be summarized using descriptive statistics.

Study medication taken (# of capsules) will be summarized using descriptive statistics.

Descriptive statistics will be presented separately by treatment group for the overall compliance to study medication. The overall compliance categories

- <= 80%,
- >80 – <= 100%, and
- >100%

will be summarized using frequency and percent by treatment.

Additionally, the individual table will be provided for

- study medication taken (capsules)and overall compliance on Day 1 i.e., two oral doses in the first day of treatment.
- study medication taken (capsules) and overall compliance after Day 1 i.e., a single daily oral dose of patients for two weeks.

All the patient's data will be listed.

The following derivation rules will be applied:

Total duration of exposure (days) = (Treatment end date – Treatment start date) + 1.

- Overall Compliance (%)= (number of capsules taken / expected number of capsules to be taken during the study (i.e.,30)) *100
- Overall Compliance on Day 1 (%) = (number of capsules taken in first day / expected number of capsules taken in first day intake (i.e., 4)) *100
- Overall Compliance after Day 1 (%) = (number of capsules taken after the first day / expected number of capsules to be taken after the first day (i.e., 26) *100

14 ANALYSES OF EFFICACY VARIABLES

14.1 EFFICACY ANALYSES

NEWS score evaluation will be performed at T0, T7, T14 and T28. NEWS score and NEWS score parameters as per collected in CRF will be provided in Listing for FAS population. Refer Appendix 3 for NEWS score.

Table 3: Summary of Analyses Strategies for efficacy endpoints:

Endpoint	Analysis set	Statistical method	Factors/Covariates	Missing data Handling	Analyses type
Virologic outcome - Proportion of patients with undetectable SARS-CoV-2 at PCR at day 7 after randomization.	FAS	Binary Logistic regression	Treatment, center, age and status	Missing data will not be imputed	Primary analysis
Virologic outcome - Proportion of patients with undetectable SARS-CoV-2 at PCR at day 7 after randomization.	PP	Binary Logistic regression	Treatment, center, age and status	Missing data will not be imputed	Sensitivity analysis
Clinical outcome - Proportion of patients who does not require supplemental oxygen therapy (NEWS ≤2) and/or mechanical ventilation at day 14 after randomization.	FAS	Binary Logistic regression	Treatment, center, age, status and baseline NEWS	Missing data will not be imputed	Primary analysis
Clinical outcome - Proportion of patients who does not require supplemental oxygen therapy (NEWS ≤2) and/or mechanical ventilation at day 14 after randomization.	PP	Binary Logistic regression	Treatment, center, age, status and baseline NEWS	Missing data will not be imputed	Sensitivity analysis

14.1.1 PRIMARY EFFICACY ENDPOINTS AND ANALYSES

1. Proportion of patients with undetectable SARS-CoV-2 at PCR at day 7 after randomization (virologic endpoint). This endpoint will be derived as below.
    - Based on Approved molecular test (PCR) result at day 7, the responses will be considered as “detectable” if PCR result is “Positive” otherwise “undetectable” if PCR result is “Negative” (Missing PCR result will be considered as missing in the main analysis).

The response (detectable / undetectable) at day 7 will be analysed using Binary logistic regression model with treatment group and pre-defined baseline factors (center, age, status and their interaction effects with treatment group). Odds ratio

will be computed for comparisons of each active treatment group versus placebo. i.e., raloxifene (60 mg) versus placebo and raloxifene (120 mg) versus placebo.

2. The proportion of patients who does not require supplemental oxygen therapy (NEWS ≤2) and mechanical ventilation at day 14 after randomization (clinical endpoint). This endpoint will be derived as below.

    - If collected NEWS score >2 or mechanical ventilation at day 14 result "Yes" then the response will be considered as "Required". If collected NEWS score ≤ 2 and mechanical ventilation with result "No" then the response will be considered as "Not Required" (if both NEWS score and mechanical ventilation are missing, patient will be considered as missing).

The response (Required/ Not required) at day 14 will be analysed using Binary logistic regression model with treatment group and pre-defined baseline factors (center, age, status, baseline NEWS and their interaction effects with treatment group). Odds ratio will be computed for comparisons of each active treatment group versus placebo. i.e., raloxifene (60 mg) versus placebo; and raloxifene (120 mg) versus placebo.

For both virologic and clinical endpoint, Binary Logistic regression will be performed using PROC GENMOD in SAS® on the observed data only to estimate difference in proportions between each active treatment versus placebo and its corresponding 95% (2-sided) confidence intervals. Exponential transformation will be used to obtain the odds ratio and corresponding 95% confidence interval. P-values will be reported based on the Wald tests from Type III analyses. Bonferroni method will be considered to handle multiple treatment comparisons.

In the SAS® procedure PROC GENMOD, a Type III analysis will be performed by adding the model options: TYPE3, DIST=BIN and LINK=LOGIT.

If the model does not converge then the following steps will be performed subsequently:

- PROC GENMOD with EXACT statement will be used.
- If the model still does not converge, then remove the factors/covariates from the model one by one (according to statistical significance) until convergence reached.
- If the model still does not converge, then perform the Fisher's exact using the SAS procedure PROC FREQ without adjusting for any pre-defined factor and covariates.

The following hypotheses will be tested:

- The null hypothesis for the virologic endpoint is that proportion of treated patients with undetectable SARS-CoV-2 at PCR at day 7 after randomization ($\pi_{RALOXIFENE}$) is lower or equal the placebo one ($\pi_{PLACEBO}$). Two sets of null and alternative hypotheses are provided, one for each treatment dosage:

$H_{01\text{-}60mg}$: $\pi_{RALOXIFENE\text{-}60mg} \leq \pi_{PLACEBO}$ $H_{01\text{-}120mg}$: $\pi_{RALOXIFENE\text{-}120mg} \leq \pi_{PLACEBO}$

$H_{11\text{-}60mg}$: $\pi_{RALOXIFENE\text{-}60mg} > \pi_{PLACEBO}$ $H_{11\text{-}120mg}$: $\pi_{RALOXIFENE\text{-}120mg} > \pi_{PLACEBO}$

- The null hypothesis for the clinical endpoint is that proportion of treated patients who does not require supplemental oxygen therapy (NEWS ≤2) and/or mechanical ventilation at day 14 after randomization ($T_{RALOXIFENE}$) is lower or equal the placebo one ($T_{PLACEBO}$). Two sets of null and alternative hypotheses are provided, one for each treatment dosage:

$H_{02\text{-}60mg}$: $T_{RALOXIFENE\text{-}60mg} \leq T_{PLACEBO}$ $H_{02\text{-}120mg}$: $T_{RALOXIFENE\text{-}120mg} \leq T_{PLACEBO}$

$H_{12\text{-}60mg}$: $T_{RALOXIFENE\text{-}60mg} > T_{PLACEBO}$ $H_{12\text{-}120mg}$: $T_{RALOXIFENE\text{-}120mg} > T_{PLACEBO}$

Superiority of raloxifene will be established if at least one null hypothesis is rejected.

The frequency and percent will be presented by treatment and visit for both primary endpoints results.

The following figures will be produced for both primary endpoints results:

- Bar chart for Proportion of Patients with undetectable SARS-CoV-2 at PCR by treatment and visit
- Bar chart for Proportion of Patients who does not require supplemental oxygen therapy (NEWS ≤2) and/or mechanical ventilation by treatment and visit

The following listings will be presented:

- Listing for the Nasopharyngeal Swab Test (PCR) results
- Listing for the supplemental oxygen therapy (NEWS ≤2) and/or mechanical ventilation

Refer the Appendix 3 for NEWS score.

14.1.2 SECONDARY EFFICACY ENDPOINTS AND ANALYSES

1. Proportion of patients with undetectable SARS-CoV-2 at PCR at day 14 after randomization at day 28 after randomization. Analyses will be performed on FAS population. This endpoint will be derived as below
    - Based on Approved molecular test (PCR) result, the responses will be considered as “detectable” if PCR result is “Positive” otherwise “undetectable” if PCR result is “Negative” (Missing PCR result will be considered as missing).

The response (detectable / undetectable) at day 14 and day 28 will be analysed using repeated measures logistic regression model with treatment group, visit and pre-defined baseline factors (center, age and status). Odds ratio will be computed for comparisons of each active treatment group versus placebo at each assessment day i.e., raloxifene (60 mg) versus placebo; and raloxifene (120 mg) versus placebo. Analyses will be performed on FAS population using observed data only.

2. Proportion of patients who does not require supplemental oxygen therapy (NEWS ≤2) and mechanical ventilation at day 7 and 28 after randomization. This endpoint will be derived as below

- If collected NEWS score > 2 or mechanical ventilation with result “Yes” then the response will be considered as “Required”. If collected NEWS score ≤ 2 and mechanical ventilation with result “No” then the response will be considered as “Not Required” (if both NEWS score and mechanical ventilation are missing, patient will be considered as missing).

The response (Required / Not Required) at day 7 and day 28 will be analysed using repeated measures logistic regression model with treatment group, visit and pre-defined baseline factors (center, age, status and baseline NEWS). Odds ratio will be computed for comparisons of each active treatment group versus placebo at each assessment day. i.e., raloxifene (60 mg) versus placebo; and raloxifene (120 mg) versus placebo. Analyses will be performed on FAS population using observed data only.

For the above two secondary endpoints, Repeated Measures Logistic regression will be performed using PROC GENMOD in SAS® on the observed data only to estimate difference in proportions between each active treatment versus placebo and its corresponding 95% (2-sided) confidence intervals. Exponential transformation will be used to obtain the odds ratio and corresponding 95% confidence interval. P-values will be reported based on the Wald tests from Type III analyses.

In the SAS® procedure PROC GENMOD, a Type III analysis will be performed by adding the model options: TYPE3, DIST=BIN and LINK=LOGIT. REPEATED statement will be used to consider visit and TYPE=UN option used for correlation-matrix. If the model does not converge then appropriate TYPE would be applied for correlation-matrix.

The following time-to-event endpoints will be analysed according to SAP section 4.4 methods.

i. Time to reach undetectable SARS-CoV-2 at PCR
ii. Time to get relieved from supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation
iii. Overall survival

Analyses will be performed on FAS population.

3. Proportion of patients in each NEWS category at Day 7, 14 and 28 after randomization will be summarized by frequency and percent by treatment and visit for FAS population.

4. NEWS score at Day 7, 14 and 28 after randomization will also be summarized using descriptive statistics by treatment and visit for FAS population.

5. Proportion of hospitalized patients who at the beginning of the study were at domicile isolation at day 7, 14 and 28 after randomization will be analysed using comparison of proportions (i.e comparisons of each active treatment group versus placebo at each assessment day) through Fisher’s exact test and will be summarized using frequency and percent by treatment and visit. Analyses will be performed on FAS population.

6. Proportion of patients admitted to intensive care at Day 7, 14 and 28 after randomization will be analysed using comparison of proportions (i.e comparisons of each active treatment group versus placebo at each assessment day) through Z-test and will be summarized using frequency and percent by treatment and visit. Analyses will be performed on FAS population.

7. Overall survival will be analysed according to time-to-event methods described in SAP section 4.4.

8. Quality of life questionnaire (EQ-5D-5L) at 3 months after the randomization will be summarized using appropriate descriptive statistics by treatment. The number and proportion of subjects of each level (1 - no problems, 2 - slight problems, 3 - moderate problems, 4 - severe problems, 5 - extreme problems) for each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be reported.
   Analyses will be performed on FAS population.

Patient's data will be listed for all secondary endpoints.

Additionally, conformed SARS-COV-2 infection listing will be provided for ENR population. Confirmation of SARS-CoV-2 infection must be available before the screening visit i.e Pre-screening. Only diagnosed COVID-19 paucisymptomatic patients will be evaluated for the trial participation.

14.1.3 DERIVATION

Pre-menopausal status – Female patients with child-bearing potential will be considered.

Post-menopausal status – Female patients with non-child-bearing potential will be considered.

Status – Male, Female with pre-menopausal status and Female with post-menopausal status will be considered for "Status" variable derivation for the Analysis.

Time to reach undetectable SARS-CoV-2 at PCR:

Patients who have experienced the event (undetectable SARS-CoV-2 at PCR), their date of PCR result confirmation will be used for time duration calculation.

Time to reach undetectable SARS-CoV-2 at PCR = (Date of undetectable SARS-CoV-2 at PCR / Censored date – Treatment Start date) + 1

Time to get relieved from supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation:

Patients who have experienced the event (relieved from supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation), their date of confirmation will be used for time duration calculation.

Time to get relieved from supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation = (Date of relieved from supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation / Censored date - Treatment Start date) + 1

Overall Survival:

Overall Survival = (Date of Death / Censored date - Treatment Start date) + 1

15 ANALYSIS OF SAFETY VARIABLES

For the safety analysis, the SAF population will be used.

Parameters for Assessment of Safety as follows:

- Adverse Events (AE) assessment
- Vital signs
- Laboratory parameters: Blood (haematology & biochemistry), Coagulation, Virology and Other marker

15.1 ADVERSE EVENTS (AE) ASSESSMENT

15.1.1 DERIVATION

AEs started before administration of study treatment will be considered as Pre-treatment AEs. Any AE started on or after the date of the first dose of study medication or started prior to first dose and worsened in severity after the first dose will be considered as Treatment-Emergent Adverse Event (TEAE). If the start date is missing for an AE, the AE will be considered as treatment emergent.

15.1.2 ADVERSE EVENT ANALYSIS

All AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) according to The Medical Dictionary for Regulatory Activities (MedDRA) September 2020, version 23.1.

Pre-treatment AEs will be presented in the listings only.

- Proportion of patients with any adverse event (grade ≤ 2 according to CTCAE) within Day 7, 14 and 28 after randomization will be analysed using comparison of proportions (i.e comparisons of each active treatment group versus placebo at each assessment day) through Fisher's exact test and will be summarized using frequency and percent by treatment and visit. Analyses will be performed on FAS population.

- Proportion of patients with severe adverse events (grade ≥ 3 according to CTCAE) within Day 7, 14 and 28 after randomization will be analysed using comparison of proportions (i.e comparisons of each active treatment group versus placebo at each assessment day) through Fisher's exact test and will be summarized using frequency and percent by treatment and visit. Analyses will be performed on FAS population.

TEAE summaries will be presented, displaying frequencies and Percentages of patients reporting AEs within each SOC in decreasing order of total frequency according to the number of patients reporting the SOC and the AE within the SOC by treatment. Along with AEs, incidence will be reported. On each of these

summaries, patients will be counted only once per SOC, even if they experience multiple AEs within the same SOC. Patients will be counted only once per preferred term, even if they experienced the same adverse event more than once.

For the summary by severity (Mild, Moderate, Severe, Life-threatening or disabling, Death), patients will be classified by the most severe level of the adverse event experienced when they experienced the same adverse event (or AE within SOC) more than once.

The severity of AEs and SAEs will be graded using the CTCAE version 5.0. Any AE not listed in the CTCAE will be graded as follows:

1. Mild
2. Moderate
3. Severe
4. Life-threatening or disabling
5. Death

For summaries, the drug-event relationship will be assessed as “None”, “Unlikely”, “Possible” “Probable” or “Highly probable”. Any AE reported in the study having a possible, probable or highly probable relationship to study drug will be defined as “Adverse Drug Reaction” (ADR).

The following events will be considered adverse events of special interest:

- Venous thromboembolic events (including deep vein thrombosis)
    - pulmonary embolism
    - retinal vein thrombosis
    - superficial vein thrombophlebitis
- Arterial thromboembolic reactions
- Thrombocytopenia

TEAEs will be reported on a per-patient basis: even if a patient reported the same event repeatedly (i.e., events mapped to the preferred term) the event will be counted only once.

The following tables will be provided separately for all TEAEs by treatment.

1) An overview of TEAEs including,

- at least one TEAE
- at least one TESAE
- at least one non-serious TEAE
- at least one ADR
- at least one serious ADR
- number of TEAEs
- number of TESAEs
- number of non-serious TEAEs

- number of ADRs
- number of serious ADRs
- number of deaths
- number of patients who discontinued study drug due to a TEAE

2) Summary of TEAEs by Primary System Organ Class and Preferred Term
3) Summary of TEAEs by Primary System Organ Class, Preferred Term and Severity
4) Summary of TESAEs by Primary System Organ Class and Preferred Term
5) Summary of ADRs by Primary System Organ Class and Preferred Term
6) Summary of TEAEs leading to Study Drug Discontinuation by Primary System Organ Class and Preferred Term
7) Summary of TEAEs leading to Death by Primary System Organ Class and Preferred Term
8) Summary of Adverse Event of Special Interest (AESI) by Primary System Organ Class and Preferred Term
9) Listing of all AEs by Patient
10) Listing of SAEs by Patient
11) Listing of Adverse Drug Reactions by Patient
12) Listing of Deaths
13) Listing of AESI

15.2 VITAL SIGNS

The following vital signs (blood pressure [BP], pulse rate [PR], body temperature [BT]), transdermal oxygen saturation (SpO2) will be collected for patients.

Vital signs measurements will be summarized by treatment using descriptive statistics for each available visit, including change from baseline.

All vital signs findings will be listed, including data from the unscheduled visits.

15.3 LABORATORY PARAMETERS: BLOOD (HEMATOLOGY & BIOCHEMISTRY), COAGULATION, VIROLOGY AND OTHER MARKER

The following biomarker parameters at Day 7, 14, 21 and 28 after randomization will be summarized using descriptive statistics by visit and treatment:

- Complete blood cell counts
- Hepatic function (ALT, AST and bilirubin)
- Coagulation (PT, aPTT and INR)
- Other marker including (D-dimer, CPK, LDH)

Depending on the nature of the variable (continuous or categorical) the change from baseline values or shift tables comparing baseline and each post-baseline qualitative results of laboratory findings will be presented.

Mean (+/-) Standard Error Plot will be plotted for the change from baseline results of the above-mentioned laboratory parameters by visit and treatment. Analyses will be performed on SAF population.

Actual results and change from baseline for quantitative laboratory parameters will be summarised descriptively by treatment and visits. In addition, shift tables for laboratory parameters comparing values (Low, Normal and High) using the standard reference ranges will be presented for the baseline laboratory measurements vs. each post-baseline visit measurements.

Additionally, the frequency of patients reporting an abnormal or abnormal clinically significant laboratory value will be presented for each laboratory parameter.

For any Patient, if more than 1 results per visit and per lab parameters are available then the latest one will be considered based the date and time.

All laboratory results will be listed.

The below list of lab parameters results will be collected for patients.

Table 4: List of Lab parameters

Biochemistry (T0, T7, T14, T21, T28)	**Haematology (T0, T7, T14, T21, T28)**	**Coagulation (T0, T7, T14, T21, T28)**
Sodium Potassium Chloride Urea Uric acid Creatinine Calcium Inorganic phosphorus Total and direct bilirubin Total protein Albumin Alpha-1 Globulins Alpha-2 Globulins Beta Globulins Alkaline phosphatase AST ALT Gamma glutamyl transferase Total Cholesterol Triglycerides	Haemoglobin Red cell count Packed cell volume Mean cell volume Mean cell haemoglobin Mean cell haemoglobin concentration Platelet count White cell count Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Prothrombin time Activated partial thromboplastin time INR
Virology (T7, T14, T28)	**Other markers (T0, T7, T14, T21, T28)**	
PCR	D-dimer Creatine phosphokinase (CPK) Lactate dehydrogenase(LDH)	

16 PREGNANCY TEST OVER THE STUDY

Data will be summarized for the SAF population. Pregnancy tests will be performed at T0, T7 and T14 visits.

A summary table showing test results (Negative/Positive) over the study will be produced by treatment group.

17 GENERAL PROGRAMMING SPECIFICATIONS

Tables, Figures and Listings will be generated as per the shells template.

All statistical analysis and output will be generated using SAS, all the reports will be printed in RTF format. All output will be in landscape orientation.

Table Format Specification:

a. In summary tables of quantitative variables, the minimum and maximum statistics will be presented to the same number of decimal places as the raw (observed) data. The estimated mean and median for a set of values will be reported to one more decimal place than the raw (observed) data and rounded appropriately. The standard errors (or standard deviations [SD]) and the confidence intervals will be reported to two additional decimal places than the raw (observed) data and rounded appropriately.

b. Data in columns of a table will be formatted as follows:
   i. Alphanumeric values will be left-justified (in mixed and upper- and lower-case)
   ii. Whole numbers (e.g. counts) will be right justified
   iii. Numbers containing fractional portions will be decimal aligned

c. All fractional numeric values will be reported with a zero to the left of the decimal point (e.g. 0.12-0.3).
d. In summary tables of qualitative variables, counts and percentages will be used. The denominator for each percentage will be the number of patients within the population under respective treatment group unless otherwise specified. Percentages will be reported to one decimal places

e. When no data are available for a table or Listings or figures, an empty page with the title will be produced with suitable text. Example: THERE WERE NO SERIOUS ADVERSE EVENTS.

f. The default tables, figures and listings (TFL) layout will be as follows

Orientation	Landscape
Paper Size	A4
Margins	Top: 2.5 cm Bottom: 2.5 cm Left: 2 cm Right: 2 cm
Font	Courier new8-point

Headers	1. The header will appear on the top left corner of each page of the output, containing the protocol number (RLX0120) and sponsor name (Dompé). The page number, in the format of "Page x of y", will appear on the top right corner of the output, where y = last page of corresponding output. Table status (draft or final). 2. Any TFLs generated prior to database lock or completion of TFL validation will be marked "Draft".
Footers For Tables	The SAS program name, Reference Listings and the date and time of the creation of the output (run date and time) will appear on the bottom left corner as follows: 1. Reference Listings: listing Number 2. Source:[program name].sas, Run on : DDMMMYYY:hh:mm:ss
Footers For Listings and Graphs/Figures	The SAS program name, and the date of the creation of the output (run date) and CRF Source will appear on the bottom left corner as follows: 1.CRF Source: 2.Source: [program name]. sas, Run on DDMMMYYYY

18 CHANGES FROM PROTOCOL

Following are the changes from the protocol:

a. Specification of additional populations-All Patient Enrolled (ENR) and Randomized Population (RND).
b. Text "Subjects", "Participants" changed to "Patients".
c. Baseline characteristics "gender" and "Child-bearing potential status" are combined and derived a new categorical variable with categories Male, Female pre-menopausal status and Female post-menopausal status to be included as factor "Status" in the statistical model of analysis of efficacy endpoints.
d. Due to the premature interruption of the enrolment, no interim analysis will be done.

19 REFERENCES

1. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic.
2. Protocol No. RLX0120, Version No.: 3.0, dated 22 Dec 2020 and RLX0120 eCRF Final v.2.0, dated 20 Jan 2021
3. ICH-E3. (December 1995). Structure and content of clinical study reports. Step 4 Guideline.
4. ICH-E6. (17 July 1996). Guideline for good clinical practice. Step 5 Guideline.
5. ICH-E9. (5 February 1998). Statistical principles for clinical trials. Step 4 guideline.
6. Support SAS® - https://support.sas.com/kb/42/728.html
7. SAS EXAMPLES - http://users.stat.ufl.edu/~aa/cda/Sas_web.pdf
8. PROC GENMOD with GEE to Analyze Correlated Outcomes Data Using SAS https://stats.idre.ucla.edu/unlinked/sas-logistic/proc-logistic-and-logistic-regression-models/
9. https://www.lexjansen.com/wuss/2006/tutorials/TUT-Smith.pdf

10. Survival Analysis
https://sphweb.bumc.bu.edu/otlt/mph
modules/bs/bs704_survival/BS704_Survival5.html
11. PharmaSUG 2013 - Paper SP03 , Combining Analysis Results from Multiply Imputed Categorical Data
12. https://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP03.pdf

20 REVISION HISTORY

Revision	Date	Description

21 APPENDIX 1: PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times:

Depending on data available, dates and times will take the form ddmmmyyyyhh:mm:ss (i.e. 01MAR2019 10:20:15)

Listings:

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output)
- Patient ID
- Date, Visit (where applicable)
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'

In all listings missing data will be reported, according to the variable type as follows:

- Character variables and dates will be presented as empty fields
- Numerical variables will be presented with a "- "

For Tables:

If any of the tables has missing summary statistics or estimate, then report it as "NE" and add a note in the bottom of the table as NE = Not Estimable, not enough data to estimate the parameter

22 APPENDIX 2: PARTIAL DATE CONVENTIONS

22.1 ALGORITHM FOR ADVERSE EVENTS

22.1.1 ADVERSE EVENT END DATE IMPUTATION

If the AE end date "**Month**" is missing, then the imputed end date "**Month**" should be set to the earliest of the (Cutoff date, End of study date, 31DECYYYY).

If the AE end date "**Day**" is missing, the imputed end date "**Day**" should be set to the earliest of the (Cutoff date, End of study date, last day of the month).

If AE "**Year**" is missing or AE is "**Ongoing**", the end date will not be imputed.
If the imputed AE end date is before the corresponding AE start date, then the AE end date will be set to the AE start date.

22.1.2 ADVERSE EVENT START DATE IMPUTATION

Adverse events with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or after the month and year of the initial study treatment date.

Partial AE start dates are imputed with reference to the treatment start date (TRTSDT) as outlined in the Imputation table below.

First find the AE start reference date, before imputing the AE start date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = minimum (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Completely missing, start dates will not be imputed. As a conservative approach, such adverse events will be defined as treatment emergent.

The date value is split into Day, month, year sections and referenced in the imputation table as outlined below	Day	Month	Year
Partial AE Start Date	01 or 15	MMM	YYYY
Treatment Start Date (TRTSDT)	Not considered	TRTM	TRTY

The following matrix explains the logic behind the imputation:

	MMM Missing	MMM < TRTM	MMM = TRTM	MMM> TRTM
YYYY Missing	NI	NI	NI	NI
YYYY < TRTY	(D)= 01JULYYYY	(C) = 15MMMYYYY	(C) = 15MMMYYYY	(C) = 15MMMYYYY
YYYY = TRTY	(B) = AE start reference date + 1 day	(C) = 15MMMYYYY	(A) = TRTSDT +1	(A) = 01MMMYYYY

YYYY > TRTY	(E) = 01JANYYYY	(A) = 01MMMYYYY	(A) = 01MMMYYYY	(A) = 01MMMYYYY

The following table is the legend to the logic matrix

Relationship	
Before Treatment Start	Partial date indicates AE start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date
Imputation Calculation	
NI	No Imputation
(A) After Treatment Start or Uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	AE start reference date+1
(C) Before Treatment Start	15MMMYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

22.2 ALGORITHM FOR CONCOMITANT MEDICATIONS:

22.2.1 CONCOMITANT TREATMENT END DATE IMPUTATION

If the concomitant treatment end date year value is missing, the date uncertainty is too high to impute a reliable date. Therefore, if the concomitant treatment end year value is missing or ongoing, the imputed concomitant treatment end date is set to NULL.

Else, if the concomitant treatment end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date31DECYYYY).

If the concomitant treatment end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month).

If the imputed concomitant treatment end date is before the existing concomitant treatment start date, use the concomitant treatment start date as the imputed concomitant treatment end date.

22.2.2 CONCOMITANT TREATMENT START DATE IMPUTATION

In order to classify a medication as prior and prior/concomitant, it may be necessary to impute the start date. Completely missing start dates will be set to one day prior to treatment start date.

As a conservative approach, such treatments will be classified as prior and concomitant (and summarized for each output). Concomitant treatments with partial start dates will have the date or dates imputed.

Partial concomitant treatment start dates are imputed with reference to the treatment start date (TRTSDT) in accordance with the rules outlined below

The date value is split into day, month, year sections and referenced in the imputation table as outlined below	Day	Month	Year
Partial CMD Start Date	01 or 15	MMM	YYYY
Treatment Start Date (TRTSDT)	TRTD	TRTM	TRTY

The following matrix explains the logic behind the imputation:

	MMM Missing	MMM < TRTM	MMM = TRTM	MMM > TRTM
YYYY Missing	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY < TRTY	(D) = 01JULYYYY	(A) = 15MMMYYYY	(A) = 15MMMYYYY	(A) = 15MMMYYYY
YYYY = TRTY	(C) Uncertain	(A) = 15MMMYYYY	(C) Uncertain	(B) = 01MMMYYYY
YYYY > TRTY	(E) = 01JANYYYY	(B) = 01MMMYYYY	(B) = 01MMMYYYY	(B) = 01MMMYYYY

The following table is the legend to the logic matrix

Relationship	
Before Treatment Start	Partial date indicates CMD start date prior to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date
Imputation Calculation	
NI	No Imputation
(A) Before Treatment Start	15MMMYYYY
((B) After Treatment Start	MAX(01MMMYYYY, TRTSDT+1)
(C) Uncertain	TRTSDT-1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

23 APPENDIX 3: NEWS SCORE

Element	Score						
	3	2	1	0	1	2	3
Respiratory rate	≤ 8		9-11	12-20		21-24	≥ 25
SpO2	≤ 91	92-93	94-95	≥ 96			
Oxygen		Yes		NO			
Systolic Blood Pressure	≤ 90	91-100	101-110	111-219			≥ 220
Pulse	≤ 40		41-50	51-90	91-110	111-130	≥ 131
ACVPU				A			C,V,P,U
Temperature, ºC	≤ 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	

ACVPU: Alert, Confusion, Voice, Pain, Unresponsive

24 SIGNATURE PAGE

By signing his/her name, each individual acknowledges that he/she has prepared, reviewed, or approved this document as indicated below and based on his/her area of expertise, confirm that the document is complete and contains no obvious errors.

A'Kanimozhi

07 Jul 2021

Kanimozhi Arumugam, Study Statistician,
Agati Clinical Informatics

Date [DDMMMYYY]

Giovanni Goisis

07 Jul 2021

Giovanni Goisis, Principal Biostatistician
Dompé

Date [DDMMMYYY]