Montreal Health Innovations
Coordinating Center
A Division of the Montreal Heart Institute

MHICC

STATISTICAL ANALYSIS PLAN

Protocol number: MHIPS-003

Colchicine Cardiovascular Outcomes Trial

COLCOT

Date of Final Statistical Analysis Plan:	04APR2019
Amendment No. 1	19AUG2019
Amendment No. 2	28AUG2019

Prepared by:
Lucie Blondeau, M.Sc
Senior Biostatistician
Montreal Health Innovations Coordinating Center (MHICC)
4100 Molson, Suite 400
Montréal, QC H1Y 3N1
Phone: 514-461-1300 ext. 2135 / Fax: 514-461-1301

Signature Approval Page

By signing below, I indicate that I have reviewed the Statistical Analysis Plan in its entirety and approve its contents.

Signature: _____ Date: 2019/8/20

Jean-Claude Tardif, MD
Principal Investigator
Montreal Heart Institute

Signature: _____ Date: _____

Marie-Claude Guertin, Ph.D.
Lead, Biostatistics
MHICC

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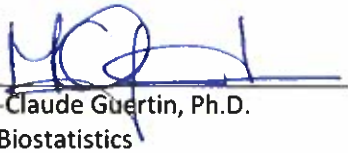
Signature:  Date: 28AUG 2019

Marie-Claude Guertin, Ph.D.
Lead, Biostatistics
MHICC

Revision History

Version	Date	Author	Summary of Changes
Amendment 1	19AUG2019	Lucie Blondeau	Section 3.3 Per Protocol Population Adding intake of study medication for < 6 months as a criterion to be excluded from the PP population. Adding that the eligibility criteria not met to be used to exclude subjects from the PP population will be those considered as important by the principal investigator. **Section 4.5** Laboratory Endpoints Adding a section for WBC and differentials that will be retrieved for a sample of subjects at Visit 2 and Visit 7. Section 5.1.1.1 Serious Adverse Events of Special Interest Adding AEs that are classified as serious adverse events under category "Cancer" to the definition of cancers and specifying the types of cancers to be analyzed. Adjusting Section 7 accordingly. **Section 6.3.7** Treatment Compliance Specifying that subjects who never took study medication will be excluded when reporting some compliance data. **Section 6.4.5** Laboratory Analysis Adding a statistical analysis for WBC and differentials. Adding the corresponding summary tables to Section 7. Section 6.4.6.2 Effect of Medication Discontinuation (On-Treatment Analysis) Adding a sensitivity analysis for the primary endpoint where subjects' follow-up will end at the date of last dose. Adding the corresponding summary table to Section 7. **Appendix 1** Adding Table 2 to describe the algorithm to derive end of study dates, Table 3 to describe the imputation rules for incomplete and/or missing date of last dose and Table 4 to describe the derivation of permanent study medication discontinuation. Minor updates, corrections and clarifications throughout the text, including in the abbreviation list.

Revision History (continued)

Version	Date	Author	Summary of Changes
Amendment 2	28AUG2019	Lucie Blondeau	**Section 6.4.1** Primary Analysis Moving former section 6.4.6.3 (Effect of Important Baseline Characteristics) to the primary analysis section to allow for an adjustment for baseline characteristics.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CEC	Clinical Endpoint Committee
CV	Cardiovascular
DOV	Date of Visit
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EOS	End of Study
GI	Gastrointestinal
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonisation
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MHICC	Montreal Health Innovations Coordinating Center
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PM	Project Manager
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Study Completion
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
WBC	White Blood Cell
WHO	World Health Organization
WLW	Wei, Lin and Weissfeld

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the final analysis of Montreal Heart Institute protocol MHIPS-003. This plan also provides a description of the tables, figures and listings that will be included in the final statistical report. It is based on the protocol dated 15NOV2018 and on the annotated case report form version 2.2. In case of differences in terms of descriptions or explanations between the SAP and the protocol, the SAP will supersede the protocol.

2 STUDY DESCRIPTION

2.1 Study Design

This will be a worldwide, randomized, double-blind, placebo-controlled, multi-center, event-driven study. Following signature of the informed consent, approximately 4500 subjects meeting all inclusion criteria and no exclusion criteria will be randomized to receive either colchicine (0.5 mg/day) or placebo (1:1 allocation ratio) for an estimated minimum of 2 years (until the target number of primary endpoint event (301) is reached). Follow-up visits or phone assessments will occur at 1, 3 and 6 months following randomization, and every 3 months thereafter for evaluation of the occurrence of any trial endpoints or other adverse events (AEs). Subjects will also be receiving standard medical care for control of dyslipidemia, hypertension, angina and diabetes. All suspected cardiovascular endpoints will be adjudicated by a clinical endpoint committee (CEC), consisting of experienced members. A fully independent 5-member Data and Safety Monitoring Board (DSMB) will be established and will review unblinded data as detailed in the DSMB charter. There will be one formal interim analysis for efficacy and futility after approximately 50% of the primary endpoints have been positively adjudicated. The DSMB charter will pre-specify the models of interim efficacy analyses and the rules for early trial termination, which will be approved by all board members. Detailed information of the interim analysis is presented in the DSMB charter dated 05-JAN-2016.

The schedule of visits for this study is outlined in Table 1 of Section 8. However, a subject may be seen at any time for safety concerns. The time window between scheduled visits is +/- 2 weeks from the anticipated scheduled dates so as to facilitate subject scheduling. Close adherence to the subject visit schedule is required in order to respect the estimated minimum 2 years of active treatment as per the protocol.

2.2 Study Objectives

The primary objective of this study is to determine whether long-term treatment with colchicine reduces rates of cardiovascular events in subjects after myocardial infarction (MI).

The secondary objective is to determine the safety of long-term treatment with colchicine in this subject population.

The tertiary objective is to evaluate links between soluble and genetic biomarkers and treatment effects.

3 DATASETS ANALYZED

Subjects who were not eligible for randomization but who have been erroneously randomized into the study will be excluded from all analysis populations. The MHICC study project manager (PM) will provide the list of all erroneously randomized subjects.

The analysis populations will be approved by the principal investigator prior to unblinding.

3.1 Intent-To-Treat (ITT) Population

The ITT population will consist of all randomized subjects (i.e. subjects having a randomization number on the Demographics electronic case report form (eCRF)). In the ITT population, subjects allocated to a treatment group by randomization will be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

3.2 Safety Population

The safety population refers to the ITT subjects who used at least one dose of study medication. The MHICC study PM will provide a log to identify all subjects who never took study medication.

Subjects will be considered as having used at least one dose of study medication if they have at least one bottle number collected on the Visit Information eCRF and if they are not listed on the MHICC study PM log.

In the safety population, subjects will be presented according to the treatment allocated by randomization. However, subjects who used any dose of the treatment opposite to the one assigned by randomization, as well as subjects randomized to placebo who used open-label colchicine, will be identified and listed.

Subjects who used any dose of the treatment opposite to the one assigned by randomization will be identified from the list of bottle treatment allocated. Information on open-label colchicine will be available from the Concomitant Medication eCRF. Open-label colchicine will be identified as concomitant medications with preferred term coded “colchicine” or “other cardiac preparations” (for pericarditis indication).

3.3 Per Protocol Population

The per-protocol population refers to the ITT subjects excluding subjects with at least one of the following major deviations:

- Never took any dose study medication;
- Took study medication for less than 6 months (i.e. subjects for whom duration of treatment exposure, as defined Section 6.5.1, is < 182 days, excluding subjects who died while being on medication [i.e. for whom # of days between date of last dose and date of death is ≤ 14 days]);
- Use of wrong treatment allocation for more than 30 cumulative days as listed in the MHICC study PM log;
- Use of open-label colchicine for more than 30 cumulative days;

- Use of chronic systemic steroids identified as concomitant medications with therapeutic subgroup (ATC2) coded “corticosteroids for systemic use”. Systemic steroids should be used more than 30 consecutive days to be classified as chronic.
- Use of erythromycin identified as concomitant medications with preferred term coded “erythromycin”.
- Use of clarithromycin identified as concomitant medications with preferred term coded “clarithromycin”.
- Eligibility criteria (inclusion/exclusion) not met as listed in the MHICC study PM log and considered as important by the principal investigator.

The duration of open label colchicine (end date - start date + 1) will be calculated for each use of open-label colchicine during the clinical study and the cumulative days will be the total of all these durations. If the cumulative days are unknown due to missing information, the worst case scenario will be applied and the cumulative days will be considered as more than 30 days.

The duration (end date - start date + 1) of each use of systemic steroid during the clinical study will also be calculated. If at least one of the durations is more than 30 days, then this systemic steroid will be classified as chronic. If at least one of the consecutive days is unknown due to missing information, the worst case scenario will be applied and the systemic steroid will be classified as chronic.

4 EFFICACY ENDPOINTS

All events that are components of the primary, secondary and exploratory efficacy endpoints will be adjudicated by an independent CEC and all definitions of the endpoints will be outlined in the CEC charter.

4.1 Primary Efficacy Endpoint

The primary endpoint will be the time from randomization to the first event of cardiovascular (CV) death, resuscitated cardiac arrest, acute myocardial infarction (MI), stroke, or urgent hospitalization for angina requiring coronary revascularization.

4.2 Secondary Efficacy Endpoints

The secondary endpoints will consist of time from randomization to the following events:

- Death (total mortality);
- Cardiovascular death;
- Resuscitated cardiac arrest;
- Acute MI;
- Stroke;
- Urgent hospitalization for angina requiring coronary revascularization;
- The first event of cardiovascular death, resuscitated cardiac arrest, acute MI or stroke.

4.3 Exploratory Efficacy Endpoints

Exploratory endpoints will consist of time from randomization to the following events:

- The first event between deep venous thrombosis or pulmonary embolus ;
- Atrial fibrillation;
- Heart failure hospitalization;
- Coronary revascularization.

4.4 Biomarker Endpoints

Frozen samples collected at Visit 2, at Visit 5 and Visit 9, and received from participating sites, will be kept for future use for evaluation of biomarkers related to cardiovascular disease and the response to treatment possibly including, but not limited to lipids, markers of inflammation and markers of oxidative stress.

Additional exploratory endpoints will include the changes in these biomarkers from baseline (Visit 2) to Visit 5, as well as a cross-sectional comparison at Visit 9 in these biomarkers. Frozen samples will be kept at the Beaulieu-Saucier Pharmacogenomics Centre of the Montreal Heart Institute.

4.5 Laboratory Endpoints (additional endpoints not specified in the protocol)

Values for white blood cells (WBC) and differentials (basophils, eosinophils, lymphocytes, monocytes and neutrophils) assessed at Visit 2 (baseline) and at Visit 7 will be retrieved for a sample of subjects. These values will come from local labs and will be expressed as absolute counts. If differentials are only available as relative values, they will be converted to absolute counts by multiplying the relative value by the absolute counts of WBC. In addition, values entered as less than a specified value will be considered as the specified value divided by 2 (e.g. entered value <0.2 will be analyzed as 0.1).

Laboratory endpoints will include the changes in these laboratory values from baseline (Visit 2) to Visit 7, calculated as the difference between the follow-up value and the baseline value.

5 SAFETY PARAMETERS

Safety in this study will be assessed by the frequency and intensity of clinical AEs.

5.1 Adverse Events

An adverse event is any unfavorable and unintended sign (including a clinically meaningful abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Information regarding AEs will be collected from the first dose of study medication (at Visit 2) through and including the last visit. Each subject will be observed and queried in a non-specific manner by the investigator or study coordinator for any new or continuing AE since the previous visit. Any AEs prior to the first dose of study medication will be recorded in the medical history and kept in the subjects' chart. All serious adverse events (SAEs) will be recorded in the appropriate eCRF section. In addition to SAEs,

the only AEs to be recorded in the eCRF are those that are either related to the gastrointestinal (GI) system, that are judged related to the study medication by the investigator or that are laboratory abnormalities judged clinically significant by the investigator. Information collected will include the onset, duration, severity, relationship to study drug, and the management. SAEs are also to be collected if they are known to occur within 30 days following the following the last study visit.

The investigator will review the clinical laboratory test results in a timely fashion when received from the laboratory. Those results qualifying as AEs as defined in section 5.1.3 will be recorded on the AE eCRF section.

Treatment-Emergent Adverse Event (TEAE) will be defined as any AE that was not present prior to randomization or that worsens in character, intensity or frequency while the subject is in an active treatment period. More specifically, TEAE will be defined as any AE with onset date ≥ date of randomization. If a partially or completely missing onset date makes the timing of an AE impossible to assess, the AE will be assumed to be treatment-emergent.

5.1.1 Serious Adverse Events

Serious adverse events are those that meet any of the following the international conference on harmonisation (ICH) criteria:

- Is fatal or immediately life-threatening;
- Results in persistent or significant disability/incapacity;
- Requires or prolongs inpatient hospitalization;
- Is a congenital anomaly/birth defect in the offspring of the subject;
- Is a cancer;
- Is an overdose (intentional or accidental);
- Is judged to be medically significant (including laboratory abnormalities).

Medically significant events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

5.1.1.1 Serious Adverse Events of Special Interest

Because of the potential effect of colchicine on cancer, new and worsening cancer will be specifically investigated. Incidence of cancer and of cancer, excluding skin cancer other than melanoma, will both be investigated.

Cancer will be identified using the Adverse Event eCRF as any adverse event falling in the MedDRA System Organ Class (SOC) term “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” or classified as a serious adverse event under category “Cancer”. Benign tumors falling in a MedDRA High Level Group Term (HLGT) containing the word “benign” will be excluded.

Cancer excluding skin cancer other than melanoma will be defined as above, but cancers falling in the MedDRA High Level Term (HLT) “Skin neoplasms malignant and unspecified (excl melanoma)” will be excluded.

5.1.2 Related Adverse Events

A related AE is one where, according to the Investigator, there is a reasonable possibility that the event may have been caused by the study drug.

5.1.3 Gastrointestinal Adverse Events

A GI AE is one that is related to the gastrointestinal system.

5.1.4 Clinical Laboratory Adverse Events

A clinical laboratory profile, including chemistry and hematology, will be performed during the study as outline in Table 1 of Section 8. Laboratory results will not be collected per se on the eCRF in this study but abnormalities in laboratory results will be collected as adverse events.

A clinical laboratory abnormality is regarded as an AE if it has been confirmed by at least 1 repeat test and suggests a disease and/or organ toxicity severe enough to require active management.

6 STATISTICAL METHODOLOGY

6.1 Determination of Sample Size

COLCOT is designed as an event-driven trial with all main analyses conducted on an intention-to-treat basis. A sample size of approximately 4500 randomized subjects with 2250 subjects in each treatment group or, in terms of events, a total number of 301 positively adjudicated events (i.e. components of the primary endpoint), would yield adequate power.

The sample size calculation is based on the primary endpoint and assumes a 30% risk reduction with colchicine, translated by a hazard ratio of 0.700. However, to account for a non-compliance rate of approximately 8% in the colchicine group, a more conservative hazard ratio of 0.724 (0.08 x 1 + 0.92 x 0.7) was used in the calculation (corresponding to a 27% relative risk reduction). Using a two-sided test at the 0.05 significance level, the trial would have 80% power if it continues until 301 positively adjudicated primary events occur in the combined treatment groups.

The total number of subjects to randomize, 4500, is chosen so that the expected number of adjudicated events after 24 months of follow-up is 301. It assumes an event rate of 7% in the placebo group at 24 months, an 18-month recruitment period during which subjects are uniformly recruited, a 24-month minimum follow-up and a 1% yearly lost to follow-up (and withdrawal of consent) rate.

The final analysis of the primary endpoint will be conducted at a significance level slightly below the 0.05 level to account for the interim analysis. However, since this will have a negligible impact on power, the sample size calculation was calculated using a significance level of 0.05.

6.2 Statistical Considerations

Baseline, efficacy and safety data will be reported using descriptive statistics. N, mean, standard deviation, median, Q1, Q3, minimum and maximum will be provided for continuous variables. Count and frequency will be provided for categorical variables.

Basic assumptions of the proposed analyses will be verified prior to the analyses. Subject disposition, datasets analyzed, baseline characteristics and efficacy analyses will be carried out on the ITT population defined in Section 3.1 according to the intent to treat principle. Safety analyses will be done on the safety population defined in Section 3.2. To account for the interim analysis, the statistical test for the primary efficacy endpoint will be two-sided and conducted at the 0.0490 significance level. All the other statistical tests will be two-sided and conducted at the 0.05 significance level. Statistical analyses will be done using SAS version 9.4 or higher.

Incomplete date of birth will be imputed for age calculation as described in Section 6.3.4.

6.2.1 Interim Analysis

An interim analysis was performed in July 2018 after 50% of the primary endpoints had been positively adjudicated (i.e. 150 positively adjudicated events). The DSMB charter specified the methods of interim analysis and the rules for early trial termination, as approved by all DSMB members. In short, the stopping rule for efficacy was based on the Lan-DeMets procedure with the O'Brien-Fleming alpha-spending function and the stopping rule for futility was based on conditional power. The interim analysis (log-rank test on the primary endpoint) was conducted at the 0.0030 significance level and the p-value for the final analysis was calculated as 0.0490. The DSMB reviewed the results of the interim analysis and recommended that the trial should continue as planned. Therefore, the final analysis will be conducted at the 0.0490 significance level.

The interim analysis was performed by the MHICC unblinded study biostatistician not otherwise involved in the study. More details about the interim analysis can be found in the DSMB charter dated 05-JAN-2016.

6.3 Study Subjects

6.3.1 Subject Disposition

Number of subjects completing the study, reasons for discontinuation and survival status at the end of the study will be summarized overall and by treatment group for the ITT population. A flow chart and a listing of subject disposition will also be provided.

The survival status information for subjects who did not complete the study and are not known to be dead will be directly obtained from the Survival Status eCRF. As for the other subjects, they will be classified as alive if they completed the study or dead if death information is known.

6.3.2 Protocol Deviations

A listing of major protocol deviations according to the MHICC study PM log will be provided.

6.3.3 Datasets Analyzed

The number of subjects in each datasets will be summarized overall and by treatment group. A listing will also be provided.

6.3.4 Demographic and Baseline Characteristics

Demographic data (age at randomization, sex and ethnic origin) and physical appearance at baseline (weight, height, body mass index (BMI) and waist circumference) will be summarized by treatment group and overall for the ITT population. BMI will be calculated as weight (kg) / [height (cm) * 0.01]^2. Delays between randomization and index MI, as well as between randomization and percutaneous coronary intervention (PCI) associated with index MI if applicable, will be presented similarly. A listing will also be provided.

For the age calculation, incomplete date of birth will be imputed as follows:

1. If the day is missing, it will be imputed to 15.
2. If the day and month are missing, they will be imputed to July 1st.
3. If the day, month and year are missing, no imputation will be done, the birth date will remain missing.

6.3.5 Medical History

Medical history details of primary interest will be the following ones: smoking (cigarettes/cigars), history of diabetes, history of hypertension, history of dyslipidemia (before index MI), prior myocardial infarction, prior PCI, prior coronary artery bypass surgery (CABG), prior Stroke/transient ischemic attack (TIA), prior heart failure and history of atrial fibrillation.

Number and proportion of subjects with these specific previous histories will be summarized overall and broken down by treatment group for the ITT population. Medical history will also be listed.

6.3.6 Concomitant Medications

The use of concomitant medication from the time of randomization and onwards will be recorded in the eCRF (with the exceptions of concomitant medication taken “when necessary” (PRN) or medication given for procedures such as coronarography). The concomitant medications will be collected in the eCRF and coded with respect to the level 2 Anatomical Therapeutic Chemical (ATC) classification and preferred term using the World Health Organization (WHO) drug dictionary (Version SEP2015).

6.3.6.1 Medication at Randomization

A medication will be flagged as being ongoing at the time of randomization if:

- Medication start date < randomization date
  AND
- (Medication end date ≥ randomization date OR Medication is ongoing)

In case of missing or incomplete medication start / end dates, the following rules will be applied:

- If 1) the medication start date is completely missing, or 2) only the year is specified, it is the same as the randomization year and randomization did not occur the first day of the year or 3) only the month/year are specified, they are the same as the randomization month/year and randomization did not occur the first day of the month, then the medication will be assumed to have started before randomization.
- If 1) the medication end date is completely missing, or 2) only the year is specified and it is the same as the randomization year or 3) only the month/year are specified and they are the same as the randomization month/year, then the medication will be assumed to have ended after randomization
- Otherwise, partial medication start / end dates (month/year or year only) will be compared to the randomization date and the medication will be classified accordingly.

Frequency of use of medications at randomization will be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment arm.

6.3.6.2 Medication at or After Randomization

Frequency of use of medications ongoing at randomization or started after randomization (i.e. all concomitant medications recorded on the eCRF) will be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment arm.

Listing of concomitant medications will also be provided.

6.3.7 Treatment Compliance

Compliance (yes/no), permanent medication discontinuation and, among subjects who did not permanently discontinued, temporary medication interruption and reduction of medication dosage since the previous visit, will be directly obtained from the eCRF at all follow-up visits (starting at Visit 5) and will be presented using number and proportion, overall and by treatment group.

Compliance (yes/no) at each visit will similarly be summarized, but excluding subjects who never took medication and subjects who permanently discontinue medication.

Number and proportion of subjects who permanently discontinued medication during the study (excluding subjects who never took medication) will be presented. Among those who did permanently discontinue medication, the duration on study medication (date of last dose of study medication – randomization date) in months will be presented, overall and by treatment group. The derivation of permanent study medication discontinuation is described in Appendix 1, Table 4.

Compliance and discontinuation will be presented for the ITT population. A listing will also be provided.

6.4 Efficacy Analysis

All suspected cardiovascular endpoints that are part of the primary, secondary and exploratory efficacy endpoints will be adjudicated by a clinical adjudication committee of experienced trialists and the statistical analysis will be conducted using positively adjudicated data (based on the CEC chair's decision Section of the Event Information eCRF).

Suspected events (based on the Event Information Section of the Event Information eCRF) as well as adjudicated events will be summarized by treatment group and overall for the ITT population. An overall cross-table will also be presented for suspected vs. adjudicated events. A listing of all events will be provided.

6.4.1 Primary Analysis

The primary endpoint of the study, time from randomization to the first event of cardiovascular death, resuscitated cardiac arrest, acute MI, stroke, or urgent hospitalization for angina requiring coronary revascularization, will be compared between the two treatment groups using a log rank test and Kaplan-Meier survival curves will be presented.

The hazard ratio from a Cox proportional hazard model will also be provided, along with a 95% confidence interval. A multivariate Cox proportional hazard model could also be contemplated to adjust for the following important baseline characteristics:

- Age;
- Sex;
- BMI;
- Delays between randomization and baseline index MI;
- Smoking;
- History of diabetes;
- History of hypertension;
- History of dyslipidemia (before Index MI);
- Prior MI;
- Prior coronary revascularization (prior PCI or prior CABG);
- Prior Heart failure.

The results from univariable Cox models with only the baseline characteristic as the dependent variable would be carefully reviewed and baseline characteristics that would 1) show an association (p-value<0.20) with the primary endpoint, 2) not have levels with too few subjects and 3) not show too many missing values would be candidate for inclusion in a stepwise multivariable Cox regression model in which the treatment group would be forced. Adjusted hazard ratios along with 95% confidence intervals would be provided.

Time to event will be calculated as the difference (in months) between the date of the first adjudicated event among the components of the primary endpoint and the date of randomization + 1 day. Death of undetermined cause will be classified as CV death for analysis purposes. Subjects with none of the events included in the primary endpoint will be censored and time to censoring will be computed as the difference (in months) between the last date subject was known to be event free (based on the Study

Completion eCRF) and the date of randomization + 1 day. The algorithm used to derive the censoring dates is described in Appendix 1, Table 2.

The primary analysis will be conducted on the ITT population and the significance level for the comparison between treatment groups will be set to 0.0490.

6.4.2 Secondary Analysis

The secondary endpoints are expressed as time from randomization to event. They will be compared between the two treatment groups using a log rank test and Kaplan-Meier survival curves will be presented. The hazard ratio from a Cox proportional hazard model will also be provided, along with a 95% confidence interval.

The secondary analyses will be conducted on the ITT population.

6.4.3 Exploratory Analysis

The exploratory endpoints are expressed as time from randomization to event and will be compared across treatment groups using the same methodology as described in Section 6.4.2.

The exploratory analyses will be conducted on the ITT population.

6.4.4 Biomarker Analysis

Blood samples for biomarkers will be collected at Visit 2 (baseline) and at Visit 5 in subjects agreeing to participate in the optional biomarkers sub-study. An additional blood samples for biomarkers will also be performed at Visit 9 in subjects agreeing to participate in this additional blood draw.

The exact biomarkers to be collected are yet to be determined but they will be analyzed as described below. Because many biomarkers are known to have a skewed distribution (ex. hs-CRP), a log-transformation is likely to be used prior to the analysis.

The changes from baseline to Visit 5 will be analyzed using an analysis of covariance (ANCOVA) model adjusting for baseline value and estimates of treatment effect will be presented with 95% confidence intervals. The biomarkers at Visit 9 will be analyzed using an analysis of variance (ANOVA) model and estimates of treatment effect will be presented with 95% confidence intervals.

The biomarker analyses will be conducted on the ITT subjects with available biomarker data. These analyses will be produced once the biomarker data will be available.

6.4.5 Laboratory Analysis

Values for WBC and differentials at Visit 2 (baseline) and at Visit 7 will be retrieved for a sample of subjects.

The change from baseline to Visit 7 will be analyzed using an ANCOVA model adjusting for the baseline value. Estimates of treatment effect will be presented with 95% confidence intervals. The ANCOVA model will be stratified by study site if the number of subjects per study site is large enough to account

for the fact that the laboratory data will come from local labs. According to the distribution of the laboratory parameters, a log-transformation might be used prior to the analysis.

The laboratory analyses will be conducted on the ITT subjects with available laboratory data.

6.4.6 Sensitivity Analysis

6.4.6.1 Effect of Major Protocol Deviations

To assess the impact of major protocol deviations, the analysis of the primary endpoint described in Section 6.4.1 will be repeated on the PP population.

6.4.6.2 Effect of Medication Discontinuation (On-Treatment Analysis)

To assess the impact of medication discontinuation, the analysis of the primary endpoint described in Section 6.4.1 will be repeated but follow-up time will end at the date of their last dose. In other words, any primary events occurring after the date of last dose will not be included in the analysis and subjects will be censored at the date of last dose if they are event free.

6.4.6.3 Robustness Checks

The Cox proportional hazards model that is presented in Section 6.4.1 assumes proportional hazards. To verify this assumption, the assessment of proportional hazard for the primary endpoint will be done by a visual inspection of the plot of log(-log(estimated Survival distribution function)) versus log time and through a formal test of the interaction between logarithm of the time variable and group at the 0.05 significance level.

6.4.7 Analysis of Recurrent Events

The primary analysis in Section 6.4.1 is based on time to first event among the components of the primary endpoint but three other analyses will be done to account for multiple events within subjects. In other words, these other analyses will make use of all events, including the ones that occur after the first. In cases of multiple events occurring the same day, the order of occurrence will be confirmed by the Medical Reviewer and coded accordingly for the statistical analysis.

The cardiovascular events that will be considered for these analyses are the components of the primary endpoint, namely:

- Cardiovascular death;
- Resuscitated cardiac arrest (non-fatal);
- Acute MI (non-fatal);
- Stroke (non-fatal);
- Urgent hospitalization for angina requiring coronary revascularization (non-fatal).

The first approach will be based on the Wei, Lin and Weissfeld (WLW) marginal model [1]. The idea behind this approach is to model the time from randomization to first, second and subsequent event with a Cox proportional hazards model and use a covariance matrix estimate for the regression

coefficients that accounts for the possible intra-subject correlation. The WLW approach can be applied when the events are of different nature and also in presence of death. In this approach, each subject is considered to be at risk for all events, regardless of how many events each subject actually experienced. This preserves the randomization and permits valid treatment effect estimation [2].

The sequence of events (CV death, non-fatal event or censoring) will be defined as in scenario II of [3]. A subject who died of a non-CV cause will be censored at the time of death. Namely, the k^{th} event of a subject (k=1, 2, …, K) will be defined as the k^{th} occurrence of a non-fatal event or CV death, whichever comes first. In this scenario, if a subject dies from a CV death before experiencing a non-fatal event, CV death will be counted K times in the combined statistic (estimated treatment effect size considered as weighted towards CV death). The number of events per subject that will be used in the analysis, K, will be set according to the number of events observed in the trial. The rule that will be considered is to choose K so that the expected number of subjects with K events is at least 5 [3]. To avoid any bias, K will be chosen prior to unblinding.

Marginal hazard ratios for a k^{th} occurrence of a non-fatal event or CV death will be provided, along with a 95% confidence interval, and tested. A weighted average of these hazard ratios will also be provided, along with a 95% confidence interval, and tested in order to examine the global treatment effect across the K events.

For illustrative purposes, number of subjects experiencing no event, 1 event, 2 events, etc. among the ones above will also be presented.

The second approach will be based on the Andersen and Gill (AG) model [4] with a robust variance estimator (sandwich estimator) [5, 6] to account for the dependency of within-subject events. This method is based on a gap-time approach considering the time since a previous event. Hazard ratio will be provided, along with a 95% confidence interval, and tested.

The first and second approaches are based on Cox proportional hazards models for time to event but a third approach will be done based on Poisson-type regressions for count data, i.e. the negative binomial regression model [7]. Number of events per subject will be used as the outcome and the length of follow-up time in months per subject will be used as an offset term in the model. For illustrative purposes, the crude event rate per 100 subjects-months by treatment group will be calculated by dividing the total number of events by the total number of follow-up months in each group and then multiplying by 100. The Negative Binomial model assumes that each subject's events follow an individual-specific Poisson rate, and that these rates vary according to a Gamma distribution. Marginal rate ratio will be provided, along with a 95% confidence interval, and tested.

These analyses will be conducted on the ITT population.

6.5 Safety Analysis

The safety analyses described in this section will be conducted on the safety population. No formal statistical testing is planned for the safety parameters.

6.5.1 Treatment Exposure

Duration of treatment exposure will be defined as number of months on treatment (computed as date of last dose – date of first study drug dispensed + 1). Duration of treatment exposure will be summarized by treatment group using descriptive statistics. Duration of treatment exposure will also be categorized according to 3-month intervals (≤ 1,]1-3],]3-6],]6-9], etc.) and summarized accordingly using frequencies and percentages, by treatment group. The imputation rules applied to incomplete and/or missing date of last dose are described in Appendix 1, Table 3.

Listing of treatment exposure will also be provided.

6.5.2 Adverse Events

Adverse events will be coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 18.1).

Number and proportion of subjects experiencing at least one treatment-emergent AE, at least one severe treatment-emergent AE, at least one treatment-emergent AE leading to study drug dosage reduced, at least one treatment-emergent AE leading to study drug temporarily interrupted, at least one treatment-emergent AE leading to study drug permanently stopped and at least one treatment-emergent AE leading to randomization code broken will be presented. In addition, number and proportion of subjects experiencing a treatment-emergent AE will be presented by system organ class, preferred term and severity for each treatment group for the safety population. In case of missing severity, the worst severity will be imputed.

Because adverse events are either categorized as SAE, SAE of special interest, AE related to study drug, GI AE or laboratory abnormality in this study, the presentation described above will be done for each category of AE.

Adverse events will also be listed.

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8 APPENDIX 1

Table 1 Timetable of Visits and Procedures
(Note: All visits are to be ± 2 weeks from anticipated timepoint)

Visits	**1 Screening Visit**	**2[a] Randomization/ Baseline**	**3 Visit**	**4 Phone contact**	**5, 7, 9… Visit**	**6, 8, 10… Phone contact**	**End of Study**
Months		**0**	**1**	**3**	**6, 12, 18…**	**9, 15, 21…**	
Informed consent	X						
Medical/Surgical history	X						
Phone contact				X		X	
Review Inclusion/Exclusion criteria	X	X					
Urine pregnancy test (only women of childbearing potential)		X					
Randomization		X					
Waist circumference, height, and weight measurements		X					
Review parameters for routine chemistry and hematology (local, once per year)		X	X[b]		X		X
Blood draw for biomarkers (optional)		X			X (V5 and V9)[c]		
Blood draw for pharmacogenomics evaluation (optional)		X[d]					X[e]
Record potential study endpoints and other AEs		X	X	X	X	X	X
Review concomitant meds	X	X	X	X	X	X	X
Study medication dispensing		X[f]	X		X		
Study medication return			X[g]		X		X

a) Screening Visit and Visit 2 may be performed on the same day; under these circumstances, procedures to be performed at both Screening Visit and Visit 2 will be performed once.
b) At V3, mandatory chemistry parameters will be evaluated locally: ALT, AST, GGT, total bilirubin, alkaline phosphatase, serum creatinine and uric acid.
c) Biomarkers collection will occur at Randomization visit and at visit 5. The additional biomarkers collection can be offered only to subjects that have yet to perform Visit 9 at the time of implementation of the sub-study at the site.
d) Blood draw for pharmacogenomics evaluation can be collected at the next in-person visit if randomization visit has already occurred at the time of the implementation of the sub-study at the site.
e) Blood draw for pharmacogenomics evaluation at the End of Study visit will only be collected for subjects who provided a baseline sample at least 12 months prior to the End of Study visit.
f) It is recommended that the subject takes his/her first dose on site during the visit.
g) Subject should bring back their 1st bottle of medication for a compliance check, but should return home with the same opened bottle (and 2nd unopened bottle assigned at V3).

Table 2 Algorithm to derive end of study dates

Calculation of time to event requires the definition of an end of study date. This date is to be used as a censoring date in event free subjects, i.e. as the date they were last known to be event free. It is to be noted that this date is to be defined differently for mortality and for other types of event.

The end date will be calculated using the following dates in the eCRF forms:

a) Date of study completion [SC Form, Date of completion where study completion = Yes]
b) Date of death [SC Form, Date of death]
c) Date of EOS visit [DOVEOS Form, Date of visit]
d) Date of last contact [SC Form, Date of last contact where study completion = No]
e) Date survival status [Survival Status Form, Last date patient known to be alive]
f) Date survival status [Survival Status Form, Date of death]

For the endpoints of death (total mortality) and CV death, the end of study date will be defined as follows:

	End of study date
In patients who completed the study as per the SC Form	Max [(a), (c)]
In patients who didn't complete the study and are dead as per the SC Form	(b)
In patients who didn't complete the study and are not dead as per the SC Form	Max [(c), (d), (e), (f)]

For all other endpoints, including composite endpoints that include CV death as a component, the end of study date will be defined as follows:

	End of study date
In patients who completed the study as per the SC Form	Max [(a), (c)]
In patients who didn't complete the study and are dead as per the SC Form	(b)
In patients who didn't complete the study and are not dead as per the SC Form	Max [(c), (d)]

Note: If the adjudicated date of death is different than the date of death reported on the SC Form, the adjudicated date of death is to be used.

Table 3 Imputation rules for incomplete and/or missing date of last dose [SC Form, Date of last dose of study medication]

It is to be noted that imputation for incomplete and/or missing date of last dose is to be done in subjects of the safety population, i.e. in subjects who took at least one dose of study medication. Subjects were asked about study medication discontinuation starting from Visit 5.

Step #1: Derive a temporary date of last dose for incomplete and/or missing date as follows:

- If only day is missing, replace missing day by last day of the month
- If both day and month are missing, replace missing day/month by 31DEC
- If date is completely missing, replace by the date of the visit at which the subject reports "permanent discontinuation since last visit" if available

Step #2: Generate the imputed date of last dose using the following dates:

a) Temporary date of last dose derived at step #1
b) Date of the visit at which the subject reports "permanent discontinuation since last visit" [DOV/DOVEOS Form, Date of visit and Compliance Form, Was the study medication permanently discontinued since the last visit at the site?]
c) Date of death [SC Form, Date of death]
d) Date of last contact [SC Form, Date of last contact where study completion = No]
e) Date of study completion [SC Form, Date of completion where study completion = Yes]

and the following imputation rules:

	Imputed date of last dose
If temporary date of last dose > date of death	(c)
If temporary date of last dose is completely missing	Max [(c), (d), (e)]
Otherwise	Min [(a), (b), (c), (d), (e)]

Note: If the adjudicated date of death is different than the date of death reported on the SC Form, the adjudicated date of death is to be used.

Table 4 Derivation of permanent study medication discontinuation

It is to be noted that permanent study drug medication discontinuation is to be assessed in subjects of the safety population, i.e. in subjects who took at least one dose of study medication. Subjects were asked about study medication discontinuation starting from Visit 5.

Permanent study medication discontinuation will be derived as follows:

- For subjects who completed a visit 5 or more, or in whom an EOS visit was done.

  Subjects who permanently discontinued study medication will be identified through the Compliance Form, using the question "Was the study medication permanently discontinued since the last visit at the site?".

- For subjects who discontinued the study prior to Visit 5 and in whom no EOS visit was done.

  Since the response to the question on permanent study medication discontinuation will be unavailable, derivation of permanent study medication discontinuation will be as follows:

		Imputed permanent study medication discontinuation
Patient is alive as per the SC Form	# of days between date of last dose and date of last contact / study discontinuation ≤ 3 days	No
	# of days between date of last dose and date of last contact / study discontinuation > 3 days	Yes
Patient is dead as per the SC Form	# of days between date of last dose and date of death ≤ 14 days	No
	# of days between date of last dose and date of death > 14 days	Yes

Note: If the adjudicated date of death is different than the date of death reported on the SC Form, the adjudicated date of death is to be used.

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