HEMOSTEMIX

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Follow up of versions

Version	Release date (dd/mm/yyyy)	Key modifications(*)	Impact

(*) Main changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Main changes from the previous signed version for the other SAP signed version(s).

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List of abbreviations

ACP	:	Angiogenic Cell Precursor
ACP-01	:	Name of Product that contains ACPs
AE	:	Adverse Event
ANCOVA	:	Analysis of Covariance
BMI	:	Body Mass Index
CI	:	Confidence Interval
CLI	:	Critical Limb Ischemia
CPH	:	Cox Proportional Hazard
ECG	:	ElectroCardioGram
HR	:	Hazard Ratio
IMP	:	Investigational Medicinal Product
ITT	:	Intent-to-Treat
LOV	:	Last Observed Value
LSM	:	Least Squares Means
MedDRA	:	Medical Dictionary for Regulatory Activities
mITT	:	Modified Intent-to-Treat
PH	:	Proportional Hazard
PI	:	Principal Investigator
PP	:	Per-Protocol
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SD	:	Standard Deviation
ST Analysis Set	:	Safety Analysis Set
VAS	:	Visual Analogue Scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses to be performed, in accordance with the main characteristics of the study protocol. The protocol version in effect at the time of this analysis was 5.5.

1.1. Study objectives

To determine the efficacy and safety of intramuscular injection of ACP-01, containing blood-derived autologous ACPs, in subjects with critical limb ischemia who are on standard of care therapy and who have no endovascular or surgical revascularization options.

1.2. Study design

This is a prospective, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of autologous ACPs administered intramuscularly into the gastrocnemius and dorsal foot muscles of one affected limb in subjects with CLI with no surgical or endovascular revascularization options.

A total of approximately 95 subjects will be randomized to treatment with ACP-01 or placebo using a 2:1 randomization scheme, respectively, stratified by site. Study will be continued until all subjects treated with the IMP have been followed for 52 weeks. One futility analysis for potentially stopping enrolment into the study was performed after approximately 42 subjects completed at least 26 weeks of follow-up. The results of this futility analysis were considered to be non-conclusive.

1.2.1. Study plan

The study consists of four periods: Screening, Treatment, safety monitoring and Long-term follow-up periods. Subjects will be followed for one year post treatment.

1.2.2. Randomisation and blinding

After a subject meets the eligibility criteria, he/she will be randomized to one of the two treatment groups, based on a randomization procedure employing a 2:1 assignment ratio, i.e., treatment with ACP-01 or placebo, respectively, using permuted blocks stratified by centers.

To enable blinding of the assessors and the subjects, the control group will undergo a similar procedure as the treatment group and receive placebo injections into the gastrocnemius and dorsal interossei foot muscles.

Blood samples and cells that are not used in the treatment of subjects with ACPs, e.g., from the placebo group, will be de-identified and may be utilized for manufacturing and quality control testing such as for the development of potency and release assays. Results from the assays and tests may be used to retrospectively examine cell and product characteristics in CLI patients and/or the response to treatment with ACPs.

The placebo will consist of a growth medium, the same medium used in the ACP product suspension. There is potential that the physician performing the administration of active treatment or placebo may become unblinded to the treatment group that the subject was randomized to while performing the injections of the IMP. Therefore, he/she will not participate in the assessment of the subjects that he/she injected. In the event that the administrator becomes

aware of the treatment assigned, every effort will be made to maintain appropriate blinding. All other participants in the study (PI, clinical investigators, other physicians, the subjects, study nurses, coordinators, etc.) will not be aware of the subjects' randomization and will therefore remain blinded to the study.

1.3. Determination of sample size

Sample size calculations were performed under the following assumptions:

- The primary study endpoint is the earlier time from treatment with study IMP to either de-novo gangrene, or doubling of wound size, or major amputation, or death.
- Randomization will allocate subjects to autologous ACPs or placebo using a 2:1 assignment ratio, respectively, stratified by site.
- The expected median time to study event as defined by the primary efficacy endpoint, assuming exponentially distributed time to event, is 3 months for placebo-treated subjects and 7 months for the ACP-treated arm.
- The anticipated monthly randomization and study IMP administration rate is 6 subjects per month.
- The minimal follow-up period of a subject will be 26 weeks if the primary endpoint is not reached, and the maximal follow-up period will be 52 weeks.
- Final analysis, under these assumptions is planned to be conducted at approximately at 22 months from first subject IMP treatment including a total of 95 subjects.
- As the effect of the early futility analysis is marginal, the final analysis will use a two-sided alpha level of 0.05

Under the above assumptions, a total of 95 subjects treated with the study IMP will provide 94% power to detect a statistically significant result at a two-sided alpha level as specified above.

The interim analysis was conducted on clinical data exported 15April2020. At the time of the 15Apr2020 data export, 65 subjects had been enrolled, treated, and followed. Subjects were enrolled in a 2:1 randomization. Follow-up ranged from 1 day to 401 days since treatment. Overall, median time-to-event was 241 days. As far as efficacy, at this stage of the clinical trial, there was not enough evidence to demonstrate that there was a difference between the two treatment groups in either the incidence or the timing of primary endpoint events.

The protocol specified that this interim analysis was to be conducted as a formal futility analysis, however this type of formal analysis was not performed. The results of this interim analysis were considered to be non-conclusive with regards to the futility objective and, therefore, the trial was allowed to proceed.

With a total of 65 evaluable subjects for final analysis, at least 51 events will be required for final analysis to detect a hazard ratio of 0.43 with 81% power at one-sided 2.5% level of significance, if the median time to study event in the placebo arm is expected to be 3 months. Power is expected to be higher if about 8 patients from South African sites are included.

2. ANALYSIS SETS AND SUBGROUPS / TREATMENT GROUPS

2.1. Analysis sets

Intent-to-Treat (ITT) Analysis Set: The intent to treat (ITT) analysis set will consist of all subjects who have been randomized to the study. In accordance with the ITT principle, all subjects randomized will be kept in their originally assigned treatment group.

Modified Intent-to-Treat (mITT) Analysis Set: The mITT analysis set is a subset of the ITT analysis set. This set will consist of data from all subjects who have been randomized to the study and administered the IMP and had at least one treatment visit post IMP administration. This analysis set will serve as the primary analysis set for efficacy inference.

Per-Protocol (PP) Analysis Set: The per protocol (PP) analysis set is a subset of the mITT analysis set and will consist of all subjects with no major protocol violations that would be considered to impact the analysis of efficacy or safety.

Safety (ST) Analysis Set: The safety analysis set (ST) will consist of all subjects who have been randomized and received the Study IMP. This analysis set will be used as the primary set for safety inference.

2.2. Treatment groups

- ACP-01
- Placebo

2.3. Subgroups

Depending on the sample size, the following subgroups will be explored: region, race, gender, age, and baseline prognostic factors (e.g., presence of ulcers at baseline and ulcer size at baseline).

3. STATISTICAL METHODS

3.1. General considerations

The following descriptive statistics will be provided depending on the nature of considered data:

Qualitative data: number of observed values, number and percentage of subjects per class.

Quantitative data: number of observed values, mean and standard deviation, median, first and third quartiles, minimum and maximum.

Descriptive summary statistics (n, mean (SD), median, min and max) will be provided for variables measured on a continuous scale.

The frequency distribution (n, %) will be provided for variables measured on a nominal scale.

3.2. Study subjects

Description of disposition of subjects (status, protocol deviations and analysis set) and baseline characteristics will be performed by treatment arm and overall.

3.2.1. Disposition of subject

Subject disposition will be tabulated for each treatment arm and overall by summarizing the number and percentage of subjects who are randomized, treated with the study treatments ACP-01 or placebo, included in each analysis set, and by the reason for early discontinuation (AE/SAE, major violation of study protocol, withdrawal of consent, lost to follow-up, death, suspected pregnancy, or other).

3.2.2. Demographic and baseline characteristics

Demographics and baseline data will be described for the mITT analysis set. Subject demographics and baseline characteristics, including underlying disease history, medical history and prior medications will be compared between the study groups to assess baseline comparability. Continuous variables (e.g., subject age, weight, height, and body mass index (BMI)) will be summarized using descriptive statistics (number [n], mean, standard deviation, and standard error, median, minimum, and maximum). Categorical variables will be summarized using subject counts and percentages. Categories for missing data will be presented if necessary.

3.2.3. Concomitant medication

All concomitant treatments taken during the treatment period will be summarized by treatment in the safety analysis set.

3.2.4. Protocol deviations

A data listing of all protocol deviations will be generated. This listing will be reviewed by the study team and each protocol deviation will be identified as major or minor.

3.3. Efficacy analysis

Efficacy analyses will be carried out in the mITT analysis set by treatment arm.

3.3.1. Primary efficacy hypothesis

The primary hypothesis of this study is that ACP-01 is superior to placebo in terms of the earlier time from treatment with IMP to either de-novo gangrene, or doubling of wound size, or major amputation, or death.

3.3.2. Primary efficacy endpoint

3.3.2.1. Definition

The primary efficacy endpoint for this study is the earlier time from treatment with IMP to either de-novo gangrene in the treated limb, or doubling of wound size in the treated limb, or major amputation in the treated limb, or death. For subjects who were lost to follow-up or completed Month 12 study visit without a study event, the time to event will be censored by the subject's last follow-up date in the study.

3.3.2.2. Primary analysis

The primary efficacy analysis will be the comparison of the distribution of time to event between the two treatment arms using a stratified log-rank test at two-sided 5% level of significance, adjusted by study site and baseline prognostic factors.

The hazard ratio (HR) and its corresponding 95% confidence interval (CI) will be estimated using a stratified Cox proportional hazard (CPH) model. Time to event for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probabilities at 3, 6, 9, and 12 months along with the corresponding 2-sided 95% CI for the estimates.

Underlying assumptions of proportional hazards will be checked using Schoenfeld Residuals test and graphical methods (Log cumulative hazard curve). The adequacy of the proportional hazards (PH) assumption will also be confirmed by including a time dependent covariate for the active treatment group by log (time) interaction in the primary analysis model and testing it using 5% significance level. If proportionality is not observed, sensitivity analyses other than those already planned in the SAP could be carried out.

3.3.2.3. Sensitivity analyses

In order to assess the consistency of the primary analysis of time to event, sensitivity analyses will be carried out including:

- An unstratified log-rank test and the hazard ratio along with the associated 95% CI resulting from an unstratified Cox model (only treatment arm in the model).
- An analysis based on PP analysis set

Three additional sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. The first sensitivity analysis assumes that subjects who discontinued without meeting any of the event criteria during the study had an event instead of being censored. The second sensitivity analysis will be based on the delta-adjusted method examined by Zhao et al. (2014). The third sensitivity analysis is an extension of the placebo-based pattern mixture model proposed by Lu (2014, 2015). The placebo-based pattern mixture model assumes that subjects who discontinued from the ACP-01 arm would have an event after discontinuation similar to that of placebo. The extended placebo-based pattern mixture model uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring underlying the placebo-based pattern mixture model. The extended placebo-based pattern mixture model sensitivity analysis for time-to-event data is described as follows:

Let $h_0(t)$ denote the baseline hazard function associated with the placebo group. Let β_1 denote the treatment effect in terms of log hazard ratios under noninformative censoring for ACP-01 versus placebo. The hazard function associated with ACP-01 under noninformative censoring is thus given by $h_1(t) = h_0(t) \exp(\beta_1)$. Consider the extended placebo-based pattern mixture model sensitivity analysis, for the placebo group, we assume that subjects with premature discontinuation would have comparable experience after discontinuation to their counterparts without premature discontinuation. For the ACP-01 treatment group, each dropout time-point for ACP-01 subjects defines a missing data pattern, and we assume that subjects with premature discontinuation would have an event after discontinuation somewhere between their counterparts without premature discontinuation and subjects in the placebo group. Specifically, we assume that $h_1(t) = h_0(t) \exp((1- \phi)\beta_1)$ for $t > C$, where C denotes the time of premature discontinuation. The sensitivity parameter $\phi \in [0,1]$ characterizes the gradual deviation from the noninformative censoring with $\phi = 0$ toward the informative censoring underlying the placebo-based pattern mixture model with $\phi = 1$. A multiple imputation approach will be used to implement the extended placebo-based pattern mixture model.

Technical details for the implementation of the sensitivity analyses are provided in Appendix I.

3.3.3. Secondary efficacy endpoints

The change from baseline in VAS pain score in the treated limb is defined at the difference between the Last Observed Value (LOV) of an individual subject subtracted from the last measurement taken prior to study IMP administration. Subjects who early terminated from the study or met the study event will be imputed a value according to the worst-case scenario; the worst recorded measurement of change of the entire study population.

The change from baseline in Ulcer Size (cm^2) in the treated limb is defined at the difference between the Last Observed Value (LOV) of an individual subject subtracted from the last measurement taken prior to study IMP administration. Subjects who early terminated from the study or met the study event will be imputed a value according to the worst-case scenario; the worst recorded measurement of change of the entire study population. In addition, Ulcer Size at baseline will be treated as zero if Ulcer is not present.

In order to control the overall Type I error rate for the primary and secondary hypotheses, the following sequential testing procedure will be implemented in the following order:

- Change from Baseline in VAS pain score in the treated limb
- Change from Baseline in Ulcer Size in the treated limb

The model baseline adjusted Least Squares Means (LSM) of the change from baseline to LOV of each of key secondary endpoints will be compared between the two study groups by applying an ANCOVA model. The model will include treatment group, study site and baseline pain measurement or baseline ulcer size measurement.

3.3.4. Subgroup analyses

Time to event subgroup analyses are planned to further explore the homogeneity of the treatment effect across patient subsets. Depending on the sample size, the subgroups, as defined in section 2.3 will be examined.

An unstratified Cox-regression model with treatment arm as predictor variable will be fitted separately for each subgroup category. The hazard ratio for treatment along with the associated 95% confidence interval will be provided.

Forest Plot of Hazard Ratios for treatment effect on time to event by selected subgroup will be provided.

The same subgroup analyses will be done for the two key secondary endpoints.

3.4. Exploratory analysis

Additional exploratory endpoints as described below will be analyzed for further exploration of the ACP treatment effect with no multiplicity adjustment. Assessments will be done for Study Week 13 and Week 26 and the exploratory outcome measures are:

- Change from baseline in the dose and quantity of analgesic drugs used by the subject
- Change from Baseline in Quality of Life (QOL)
- Change from Baseline in Ankle Pressure
- Change from Baseline in Toe Pressure
- Proportion of subjects with an improvement in VAS pain score
- Change from baseline in Ulcer Size
- Difference on change from baseline in VAS pain score between the treated limb and the untreated limb if enough data are available for meaningful inference
- Difference on change from baseline in Ulcer Size between the treated limb and the untreated limb if enough data are available for meaningful inference
- Proportion of responders based on ulcer size, pain score and QOL, based on the following 3 criteria as described below

- Reduction in the last observed ulcer size by 50%
- Decrease in the last observed pain score by >2 or more
- Improvement of the last observed QOL total score by 20%

Alternatively, to account for unequal importance of ulcer size, QOL and pain score, the composite endpoint will be the hierarchical combination of the last observed ulcer size, the last observed pain score and the last observed QOL total score. We will calculate Win-Ratio using the Finkelstein-Schoenfeld (Finkelstein 1999) scoring algorithm detailed in the table. For each matched pair, the patient is labelled a "winner" or a "loser" depending on ulcer size. If that is not known, only then they are labelled a "winner" or "loser" depending on QOL and then pain score. Otherwise they are considered tied. The win ratio is the total number of winners divided by the total number of losers. A 95% confidence interval (CI) and P-value for the win ratio can be obtained. The Win-Ratio accounts for clinical priorities, so that ulcer size is considered more important than QOL and pain score and gets first priority. The method also recognizes that patients have differing risk profiles by using risk-matched pairs and provides an informative estimate of treatment difference with CI and P-value.

Scenario	Subject: i/j	Ulcer size	QOL total score	Pain score	Score
1	i	Large	not in consideration	not in consideration	-1
	j	Small	not in consideration	not in consideration	+1
2	i	Tied	Low	not in consideration	-1
	j	Tied	High	not in consideration	+1
3	i	Tied	Tied	High	-1
	j	Tied	Tied	Low	+1
4	i	Tied	Tied	Tied	+0
	j	Tied	Tied	Tied	+0

If i and j are reversed in severity than the value assigned to i is +1.

3.5. Safety analysis

All safety analyses will be performed in the Safety analysis set.

3.5.1. Adverse events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment-related (overall and by severity), serious adverse events, adverse events causing early termination and non-serious adverse events. The incidence of adverse events will be summarized using descriptive statistics by system organ class and preferred term. Subjects are counted only once in each system organ class category, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, subjects are counted at the greatest severity. Adverse events missing the flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non serious adverse events. Listings for deaths, serious adverse events, adverse events leading to discontinuation, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by subject number will be presented.

3.5.2. Clinical laboratory evaluation

Summary statistics for laboratory tests will be presented at baseline and consecutive scheduled treatment visits. Laboratory tests results and changes from baseline to each visit and endpoint will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit and endpoint will be summarized using subject counts. The incidence of clinically significant abnormal results will also be summarized for laboratory data using descriptive statistics.

3.5.3. Vital signs

Summary statistics for vital signs will be presented at baseline and consecutive scheduled treatment visits. Vital signs values and changes from baseline to each visit and endpoint will be summarized using descriptive statistics. The incidence of clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

3.5.4. ECG

Summary statistics for ECGs will be presented at baseline and consecutive scheduled treatment visits. ECG values and changes from baseline to each visit and endpoint will be summarized using descriptive statistics. The incidence of clinically significant abnormal values will be summarized for selected ECGs using descriptive statistics.

4. STATISTICAL AND DATA HANDLING CONVENTIONS

4.1. Summary Statistics

The following statistical summaries will be presented for each type of data:

- Continuous variables will be summarized by descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum values).

- Categorical variables will be summarized by frequency distributions (counts and percentages).

- Time-to-event data will be summarized by showing the number of subjects, number of subjects experiencing the event of interest, estimates of the median, first quartile and third quartile using the Kaplan Meier estimate as well as a 95% CI for the median

4.2. Visit Time Windows

Nominal visits will be used for analysis.

4.3. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of IMP, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of IMP, a severity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

4.4. Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to the IMP is missing for an AE that started on or after the date of the first dose of IMP, a causality of yes will be assigned. The imputed values for causal relationship to randomized treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

4.5. Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for an AE is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of IMP, the month and day of the first dose of IMP will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of IMP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of IMP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of IMP, the day of the first dose of IMP will be assigned to the missing day.

- If either the year of the incomplete start date is before the year of the date of the first dose of IMP or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of IMP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of IMP or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of IMP, the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of IMP, the date of the first dose of IMP will be assigned to the missing start date.

- If the stop date is before the date of the first dose of IMP, the stop date will be assigned to the missing start date.

4.6. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e. partially missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

4.6.1. Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of IMP, the month and day of the first dose of IMP will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of IMP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of IMP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of IMP, the day of the first dose of IMP will be assigned to the missing day.

- If either the year of the incomplete start date is before the year of the date of the first dose of IMP or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of IMP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of IMP or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of IMP, the first day of the month will be assigned to the missing day.

4.6.2. Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the date of last dose of IMP, the month and day of the date of the last dose of IMP will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of last dose of IMP, *December 31* will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of last dose of IMP, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IMP, the day of the date of the last dose of IMP will be assigned to the missing day.

- If either the year of the incomplete stop date is before the year of the date of last dose of IMP or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of IMP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete stop date is after the year of the date of the last dose of IMP or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of IMP, the first day of the month will be assigned to the missing day.

5. REFERENCES

Lu K. An extension of the placebo-based pattern-mixture model. Pharmaceutical Statistics 2014; 13: 103-109.

Lu K., Li D., Koch, G. Comparison between two controlled multiple imputation methods for sensitivity analysis of time-to-event data with possibly informative censoring. Statistics in Biopharmaceutical Research, 2015; 7: 199-213.

Zhao, Y., Herring, A. H., Zhou, H., Ali, M.W., and Koch, G. G. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring," Journal of Biopharmaceutical Statistics, 2014; 24: 229–253.

Pocock, Stuart J., et al. "The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities." *European heart journal* 33.2 (2012): 176-182.

Finkelstein, Dianne M., and David A. Schoenfeld. "Combining mortality and longitudinal measures in clinical trials." *Statistics in medicine* 18.11 (1999): 1341-1354.

6. APPENDICES

APPENDIX I. TECHNICAL DETAILS FOR THE IMPLEMENTATION OF THE EXTENDED PLACEBO-BASED PATTERN MIXTURE MODEL VIA MULTIPLE IMPUTATION

The following steps will be taken to implement the extended placebo-based pattern mixture model via multiple imputation:

1. Carry out a Bayesian analysis for the Cox proportional hazards model with treatment group as an explanatory variable and with piecewise constant baseline hazard function. Let $h_0(t;\lambda) = \sum_{j=1}^{J} \lambda_j I(a_{j-1} \le t < a_j)$ denote the piecewise constant baseline hazard function, where $a_0 = 0 < a_1 < \cdots < a_{J-1} < a_J = \infty$ denotes a partition of the time axis. The cut points are chosen to have an approximately equal number of events in each interval. The number of intervals with constant baseline hazard rates, *J,* is set to strike a balance between the approximation to the unknown underlying baseline hazard function and the number of events in each interval. The hazard function for subject *i* is $h(t \mid X_i;\theta) = h_0(t;\lambda)\exp(\beta_1 X_{i1})$, where X_{i1} = 1 if subject *i* is in the ACP-01 group.

2. Take a posterior draw of the model parameters, $\tilde{\theta} = (\tilde{\lambda}, \tilde{\beta})$, from the Bayesian analysis.

3. For a subject who prematurely discontinued without meeting any of the eventcriteria during the study, impute the time to event after discontinuation, T_i, under the extended placebo-based pattern mixture model with sensitivity parameter ϕ, by equating the conditional survival probability at T_i given that the subject discontinued at C_i to a uniform random variable U_i, that is,

$$\exp\left\{-\int_{C_i}^{T_i} h_0(t;\tilde{\lambda}) e^{(1-\phi)(\tilde{\beta}_1 X_{i1})} dt\right\} = U_i .$$

   This equation can be easily solved by noting that the baseline hazard function $h_0(t; \lambda)$ is piecewise constant.

4. If the imputed event time exceeds the planned follow-up time for the subject, we manage the subject as having no event by the end of the planned follow-up time. Thus, the imputed complete data set has no subjects with premature discontinuation and has only administrative censoring at the planned follow-up time.

5. Apply the primary analysis model to the complete data set to obtain the parameter estimates and associated covariance matrix for a single imputation. The parameters are the log-rank test statistics for the log-rank test, and the log hazard ratios for the Cox model with treatment group as an explanatory variable.

6. Repeat Step 2 through Step 5 for *m* times to generate *m* sets of imputed complete-data parameter estimates and associated covariance matrices. Use the SAS procedure

MIANALYZE to combine results from *m* imputed data sets and draw inference about the treatment effect of ACP-01 versus placebo.

7. Vary the value of the sensitivity parameter $\phi \in \{0, 0.2, 0.4, 0.6, 0.8, 1\}$ in Step 3 to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption toward the informative censoring underlying the placebo-based pattern mixture model.