STATISTICAL ANALYSIS PLAN

A Randomised, Partially Double-blind, Placebo- and Positive-controlled, 4-way Crossover Study to Evaluate the Effect of Icosabutate (NST-4016) on the QT/QTc Interval in Healthy Subjects

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 26 July 2018

Study Drug: icosabutate (NST-4016)

Sponsor Reference Number: NST-01
Covance Study Number: 8383557

Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the safety and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

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Statistician

31 JUL 2018
Date

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30 JUL 2018
Date

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26 JUL 2018
Date

2 TABLE OF CONTENTS

3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ΔΔQTcF	placebo-corrected change-from-baseline QTcF
ΔQTcF	change-from-baseline QTcF
ADaM	Analysis Data Model
AE	adverse event
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of the last observed concentration
BLQ	below the level of quantification
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	maximum observed plasma concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram
HR	heart rate
ICH	International Conference on Harmonisation
NC	not calculated
NR	no result
PK	pharmacokinetic
QTc	QT interval corrected for heart rate
QTcF	Fridericia correctedQT interval
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{last}	the time of the last observed plasma concentration
T_{max}	time of the maximum observed plasma concentration

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version dated 11 April 2018).

This SAP describes the planned analysis of the safety, tolerability and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

Separate SAP describing all other planned analysis, including analysis of the ECG data will be produced by of iCardiac Technologies, Inc..

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between NorthSea Therapeutics BV and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalised, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between NorthSea Therapeutics BV and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

The primary objective of the study is:

- To evaluate the effects of therapeutic and supratherapeutic concentrations of icosabutate on the Fridericia's corrected QT interval (QTcF) in healthy subjects (this will be a responsibility of iCardiac Technologies, Inc.).

The secondary objectives of the study are:

- To evaluate the effect of therapeutic and supratherapeutic doses of icosabutate on other electrocardiogram (ECG) parameters (heart rate [HR], PR and QRS intervals, and T-wave morphology) in healthy subjects (this will be a responsibility of iCardiac Technologies, Inc.).

- To evaluate the PK of single doses of 600 mg and 2000 mg icosabutate in healthy subjects (this will be a responsibility of Covance EC Biometrics).

- To assess the safety and tolerability of single doses of 600 mg and 2000 mg icosabutate in healthy subjects (this will be a responsibility of Covance EC Biometrics).

6 STUDY DESIGN

This will be a Phase 1, single-centre, randomised, double-blind (except for moxifloxacin), placebo- and positive-controlled, 4-way crossover study assessing the ECG effects of therapeutic and supratherapeutic doses of icosabutate in healthy male and female subjects.

Thirty-two subjects will be randomised to 1 of 12 treatment sequences (Table 1), with approximately 3 subjects randomised into 8 of the 12 sequences, and 2 subjects randomised into 4 of the 12 sequences, and will receive a single oral dose of each of the following treatments, with a minimum 5-day wash-out between doses:

- therapeutic dose of icosabutate (600 mg)

- supratherapeutic dose of icosabutate (2000 mg)

- moxifloxacin (400 mg)

- placebo

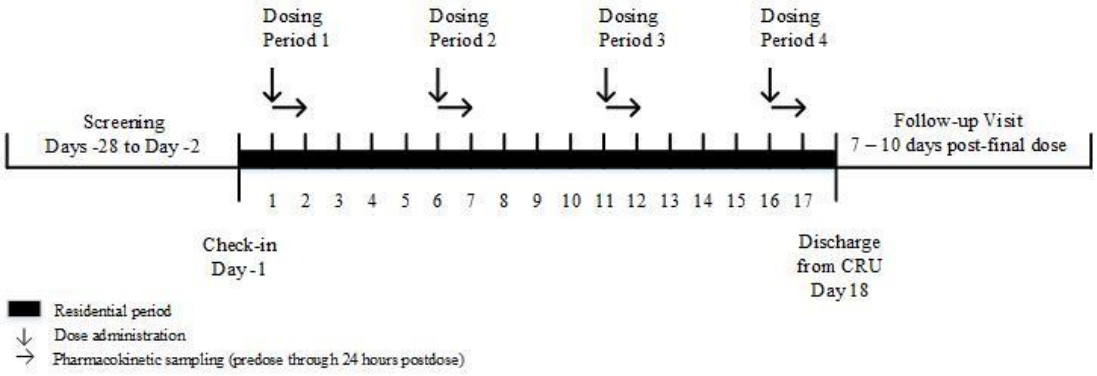
Moxifloxacin will be used as a positive control to determine the assay sensitivity of this study, with an expected peak QT effect (placebo-corrected change-from-baseline QTcF [ΔΔQTcF]) of 10 ms to 15 ms.

Table 1: Treatment Sequences

Treatment Sequence	Dosing Period			
	1 (Day 1)	**2 (Day 6)**	**3 (Day 11)**	**4 (Day 16)**
1	icosabutate (600 mg)	icosabutate (2000 mg)	placebo	moxifloxacin (400 mg)
2	icosabutate (2000 mg)	moxifloxacin (400 mg)	icosabutate (600 mg)	placebo
3	placebo	icosabutate (600 mg)	moxifloxacin (400 mg)	icosabutate (2000 mg)
4	moxifloxacin (400 mg)	placebo	icosabutate (2000 mg)	icosabutate (600 mg)
5	icosabutate (2000 mg)	placebo	icosabutate (600 mg)	moxifloxacin (400 mg)
6	placebo	moxifloxacin (400 mg)	icosabutate (2000 mg)	icosabutate (600 mg)
7	icosabutate (600 mg)	icosabutate (2000 mg)	moxifloxacin (400 mg)	placebo
8	moxifloxacin (400 mg)	icosabutate (600 mg)	placebo	icosabutate (2000 mg)
9	placebo	icosabutate (600 mg)	icosabutate (2000 mg)	moxifloxacin (400 mg)
10	icosabutate (600 mg)	moxifloxacin (400 mg)	placebo	icosabutate (2000 mg)
11	icosabutate (2000 mg)	placebo	moxifloxacin (400 mg)	icosabutate (600 mg)
12	moxifloxacin (400 mg)	icosabutate (2000 mg)	icosabutate (600 mg)	placebo

Subjects will be screened to assess their eligibility from Day -28 to Day -2. Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1 and remain in the CRU until Day 18. Each subject will participate in 4 dosing periods, with doses administered in the morning of Days 1, 6, 11, and 16 after an overnight fast of at least 8 hours (not including water). Dose administration in each dosing period will be separated by a wash-out period of at least 5 days. There will be a Follow-up Visit 7 to 10 days after the final dose administration. An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



The total duration of study participation for each subject (from Screening through Follow-up Visit) is anticipated to be approximately 8 weeks.

7 TREATMENTS

The following is a list of the study treatment and ordering that will be used in the TFLs.

Study Treatment	Order on TFLs
600 mg icosabutate	1
2000 mg icosabutate	2
400 mg moxifloxacin	3
Placebo	4

The following is a list of the study treatment sequence abbreviations and ordering that will be used in the baseline TFLs.

Study Treatment Sequence	Abbreviation	Order on TFLs
600 mg icosabutate/2000 mg icosabutate/Placebo/400 mg moxifloxacin	A/B/C/D	1
2000 mg icosabutate/400 mg moxifloxacin/600 mg icosabutate/Placebo	B/D/A/C	2
Placebo/600 mg icosabutate/400 mg moxifloxacin/2000 mg icosabutate	C/A/D/B	3
400 mg moxifloxacin/Placebo/2000 mg icosabutate/600 mg icosabutate	D/C/B/A	4
2000 mg icosabutate/Placebo/600 mg icosabutate/400 mg moxifloxacin	B/C/A/D	5
Placebo/400 mg moxifloxacin/2000 mg icosabutate/600 mg icosabutate	C/D/B/A	6
600 mg icosabutate/2000 mg icosabutate/400 mg moxifloxacin/Placebo	A/B/D/C	7
400 mg moxifloxacin/600 mg icosabutate/Placebo/2000 mg icosabutate	D/A/C/B	8
Placebo/600 mg icosabutate/2000 mg icosabutate/400 mg moxifloxacin	C/A/B/D	9
600 mg icosabutate/400 mg moxifloxacin/Placebo/2000 mg icosabutate	A/D/C/B	10
2000 mg icosabutate/Placebo/400 mg moxifloxacin/600 mg icosabutate	B/C/D/A	11
400 mg moxifloxacin/2000 mg icosabutate/600 mg icosabutate/Placebo	D/B/A/C	12

8 SAMPLE SIZE JUSTIFICATION

A total of 32 subjects will be enrolled in order that a minimum of 28 subjects complete the study. Based on experience from the IQ CSRC study[3] simulations to evaluate the power of small studies with exposure response analysis[4], and the observations from 25 recent TQT studies using exposure response analysis, a sample size of 28 will provide more than 95% power to exclude that icosabutate causes more than a 10 ms QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2 sided 90% confidence interval of the model predicted QTc effect (ΔΔQTcF) at the observed geometrical mean C_{max} of icosabutate in the study.

In addition to the evaluation through modelling and simulation, the sample size can be estimated approximately using a simple paired t-test for equivalence. Under the assumption that the QTc effect is 3 ms for icosabutate and 0 ms for placebo with a common standard deviation (SD) of change-from-baseline QTcF (ΔQTcF) of 8 ms for each treatment, and that 'No Effect' will be concluded if the 90% confidence interval of ΔΔQTcF is lower than 10 ms, 28 subjects will provide >95% power with a one sided alpha of 5% in paired t-test. This estimation was performed using the paired t-test for equivalence of Means in R Version 3.2.5.

To demonstrate assay sensitivity with exposure-response analysis, it has to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 ms (ie, the lower bound of the 2-sided 90% CI of the predicted QT interval corrected for heart rate (QTc) effect [ΔΔQTcF] should exceed 5 ms). In a similarly designed recent crossover study with 24 healthy subjects, the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the exposure-response analysis was 1.24 ms. The within-subject SD of change-from-baseline QTcF (ΔQTcF) in the referred study was 5.4 ms. If the effect of moxifloxacin is assumed to be 10 ms, the SE of 1.24 ms corresponds to an effect size of $\left({}^{(10-5)}/_{(1.24\times\sqrt{24})} \right) = 0.82$, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. In a one-sample t-test situation with a sample size of 24 subjects, this effect size results in a power of 98.8%. This value should be compared with the effect size of 0.57 required to guarantee a power of at least 90% in a one-sample t-test situation with a sample size of 28 subjects. Based on this calculation, a power of at least 90% will be obtained as long as the variability of ΔQTcF, as measured by its SD, does not exceed 7.8 ms (ie, 144% of the 5.4 ms observed in the referred study).

9 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug (icosabutate, moxifloxacin, placebo) and have at least 1 postdose safety assessment.

The **PK Population** will consist of all subjects who received at least 1 dose of study drug (icosabutate, moxifloxacin) and have evaluable PK data. A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an adverse event (AE) of vomiting that occurs at or before 2 times median time of the maximum observed plasma concentration (T_{max}), or important protocol deviations or AE thought to significantly affect the PK of icosabutate.

The **All Subjects Population** will be consistent with the Safety Population.

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics will be performed for subjects included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (eg, the PK

parameters: areas under the concentration-time curve [AUCs] and maximum observed plasma concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilised to ensure compliance with CDISC standards.

Period day (day within the dosing period) will be used throughout all TFLs. It will be derived in the ADaM datasets (where applicable) and the mapping from study day to period day will be as follows.

	Dosing Period 1					Dosing Period 2					Dosing Period 3					Dosing Period 4		
Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Period Day	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3

10.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to last dosing, including repeat (vital signs and ECGs) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings). For ECGs taken in triplicate, baseline will be the median of the last 3 values taken prior to last dosing.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where

results are taken in triplicate and repeated, the last 3 readings are used in all subsequent calculations.

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate, the original reading is defined as the first reading of the triplicate. All results not taken at a scheduled timepoint for other data types (eg, clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarised by treatment sequence and listed. Subject disposition will be summarised by treatment sequence and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible, from the plasma concentrations of icosabutate, using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 6.4 or later):

Parameter	Definition
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of the last observed plasma concentration (T_{last}), calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
C_{max}	maximum observed plasma concentration
T_{max}	time of the maximum observed plasma concentration

Additional PK parameters may be determined where appropriate.

The C_{max} for moxifloxacin will be calculated by iCardiac Technologies, Inc.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with Sponsor's approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

Both C_{max} and T_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported.

10.3.2 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

- Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;
    - Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
    - If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
    - If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
    - If a predose concentration is missing, these values may be set to zero for single dose studies and first dose of multiple dose studies with sponsor approval

10.3.2.1 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.
- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.
- PK parameters associated with positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the pharmacokineticist.

10.3.3 Presentation of Pharmacokinetic Data

10.3.3.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarised.
- For the calculation of summary statistics, BLQ values will be set to zero.

- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.

- Where there is NR, these will be set to missing.

- If there are less than three values in the data series, only the min, max, and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.

- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.

- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

- Concentrations for which actual sampling time deviated > (5 mins + 10% of nominal time) will be excluded from summary statistics.

10.3.3.2 Presentation Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

- The AUC_{0-t} values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

10.3.4 Pharmacokinetic Statistical Methodology

No inferential statistical analysis will be performed.

PK parameters and plasma concentrations of icosabutate will be summarised by treatment and listed. Plasma concentrations will be graphically represented with an arithmetic mean plot and a concentration-time profile by subject (linear scale and semi-logarithmic scale).

10.4 Safety and Tolerability Assessments

10.4.1 Adverse Events

A baseline sign and symptom is defined as an AE that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose.

All AEs will be listed. The TEAEs will be summarised by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarised by treatment, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study treatment. Any severe or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

10.4.2 Clinical Laboratory Parameters

Clinical chemistry and haematology data will be summarised by treatment. In addition, all clinical chemistry, haematology, and urinalysis data outside the clinical reference ranges will be listed by parameter and treatment.

Values for any clinical chemistry, haematology, and urinalysis values outside the clinical reference ranges will be flagged on the individual subject data listings.

10.4.3 Vital Signs

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

The absolute values and changes from baseline in vital signs data will be listed and summarised by treatment. Figures of mean vital signs and mean change from baseline profiles will be presented by treatment.

10.4.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the QTcF, the PR and QT intervals, the QRS interval, and HR.

Where ECGs are measured in triplicate (at approximately 2-minute intervals), the median value will be used in all subsequent calculations.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

The ECG data will be listed and summarised by treatment. Figures of mean ECG data and mean change from baseline profiles will be presented by treatment.

An outlier analysis will be performed including all individual postdose measurements (not the mean data), including all repeat and unscheduled readings. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarised for each treatment according to the following categories: >30, >60, and ≤30 ms. All incidences of >30 and >60 ms will be flagged on the listing. In addition, the frequency of subjects with QTcF postdose

values will be summarised for each treatment, according to the following categories: >450, >480, >500, and ≤450 ms. All incidences of >450, >480, and >500 ms will be flagged on the listing.

10.4.5 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarised or statistically analysed.

Medical history data will not be presented.

10.4.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Darpo B, Benson C, Dota C, Ferber G, Garnett C, Green CL, et al. Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther. 2015 Apr;97(4):326–35.

4. Ferber G, Zhou M, Darpo B. Detection of QTc effects in small studies--implications for replacing the thorough QT study. Ann Noninvasive Electrocardiol Off J Int Soc Holter Noninvasive Electrocardiol Inc. 2015 Jul;20(4):368–77.