STATISTICAL ANALYSIS PLAN

A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Intravenous FDY-5301 in Acute Myocardial Infarction

Statistical Analysis Plan Status: Final v1
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Study Drug: FDY-5301

Sponsor Reference Number: FDY-5301-201
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Clinical Phase 2a

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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 statistical, safety, efficacy, 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.

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3 ABBREVIATIONS

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

ADaM	analysis data model
AE	adverse event
AMI	acute myocardial infarction
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last observed quantifiable concentration
AV	Atrioventricular
BLQ	below the limit of quantification
BPM	beats per minute
CDISC	Clinical Data Interchange Standards Consortium
CL	total body clearance
C_{max}	maximum observed plasma concentration
CMR	cardiac magnetic resonance
CRF	Case Report Form
CSR	Clinical Study Report
CV%	coefficient of variation
ECG	electrocardiogram
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
FS	fractional shortening
ICH	International Conference on Harmonisation
INF	infarct size
ITT	intent-to-treat

Kel	apparent terminal elimination rate constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	myocardial salvage index
NC	not calculated
NR	no result
PCI	percutaneous coronary intervention
PK	pharmacokinetics
PP	per protocol
SAP	Statistical Analysis Plan
SD	standard deviation
STEMI	ST-segment elevation myocardial infarction
$T_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{last}	time of last quantifiable concentration
T_{max}	time when maximal concentration is achieved
V_{ss}	volume of distribution at steady-state
VV	ventricular volume
V_z	volume of distribution during the terminal elimination phase
WHO	World Health Organization

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol Final Version 1.0 dated 02 April 2017 and Final Version 2.0 dated 21 August 2017.

This SAP describes the planned analysis of the safety, efficacy, 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. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Faraday Pharmaceuticals and Covance Early Clinical 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 finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, 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 Faraday Pharmaceuticals and Covance Early Clinical 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 OBJECTIVE AND PURPOSE

The purpose of this study is to evaluate the safety, efficacy, and PK of 3 dose levels of FDY-5301 compared to placebo in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI).

6 STUDY DESIGN

6.1 Primary Outcomes

The primary outcome for this study will be the combined number and incidence rate of several arrhythmias of interest for 14 days post-study drug. The arrhythmias of interest include the following categories:

- Ventricular fibrillation

- Sustained ventricular tachycardia (heart rate [HR] ≥125 beats per minute [BPM], ≥ 30 seconds)

- Non-sustained ventricular tachycardia (HR $\geq$125 BPM, $\geq$ 16 irregular beats, < 30 seconds)

- High degree Atrioventricular (AV) block (2nd or 3rd degree, $\geq$ 8 irregular beats)

The time-to-last-event outcome for each arrhythmia of interest will be studied.

The time-to-patch-applied, derived as time duration between the start of PCI procedure and the application of the patch monitoring device will also be studied.

6.2   Secondary Outcome

6.2.1   Secondary Efficacy Outcome

The secondary efficacy outcomes for this study will be:

- Infarct size parameters assessed by CMR at 72 ±4 hours post-study drug and 3 months post-study drug

    o   Infarct size as a proportion of ventricular volume (INF/VV)

    o   Myocardial salvage index (MSI)

    o   Absolute myocardial infarction size (INF).

- Proportion of patients with ST-segment resolution at 4 hours post-study drug

- Proportion of patients with persistent arrhythmias at 30 days and 3 months post-study drug

- Measures of cardiac function by CMR at discharge (72 ± 24 hours) and 3 months for the following

    o   End-diastolic volume (EDV)

    o   End-systolic volume (ESV)

    o   Fractional shortening (FS)

    o   Ejection fraction (EF)

- Serum levels of troponin calculated as AUC over 48 hours post treatment

- Plasma biomarkers of cardiac injury, inflammation and remodeling out to 3 months of follow up

6.2.2   Secondary Safety Outcome

The secondary safety outcomes for this study will be:

- Incidence of adverse events (AEs)

- Change from baseline in physical examination results, clinical laboratory values, and vital signs values

- Incidence of all cause and cardiac mortality out to 6 months of follow up-to be assessed by phone call to patient or if patient is unavailable, by medical records of physician/investigator

6.2.3 Secondary Pharmacokinetic Outcome

Plasma concentrations of iodide will be assessed and the appropriate PK parameters calculated.

6.3 Exploratory Outcome

The exploratory outcome for this study will be:

- Incidence of newly onset atrial fibrillation during 14 days post-study drug monitoring period

7 STUDY DESIGN

This is a Phase 2A, randomized, double-blind, placebo-controlled, multi-center study that will evaluate the safety, efficacy, and PK of FDY-5301 in patients with acute STEMI undergoing PCI.

Patients will receive either FDY-5301 or volume matched placebo after informed consent is obtained and a STEMI diagnosis has been made based on clinical and electrocardiogram (ECG) findings, within an hour prior to myocardial reperfusion.

A minimum of 80 evaluable patients will be enrolled and randomized in a 1:1:1:1 ratio to receive a single dose of 0.5, 1.0, or 2.0 mg/kg FDY-5301 or placebo.

All patients will have an early and late (3 month) cardiac magnetic resonance (CMR) and 14 days of arrhythmia monitoring and will be followed up for safety and efficacy for up to 6 months. Patients will be monitored in hospital, and return for clinic visits 14 days, 30 days, and 3 months post PCI (Figure 1).

Figure 1: Study Diagram

8 TREATMENTS

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

Study Treatment Name	Treatment Order on TFLs
Placebo	1
0.5 mg/kg FDY-5301	2
1.0 mg/kg FDY-5301	3
2.0 mg/kg FDY-5301	4
Overall FDY-5301	5 (where necessary)

9 SAMPLE SIZE JUSTIFICATION

As this is the first clinical study of FDY-5301 in patients, safety is the primary focus. For this reason, the goal is to expose a limited number of patients to FDY-5301 while still powering the study to detect significant differences in efficacy measures across groups. A total sample size of 80 patients will provide 80% power to detect a 37% reduction in infarct size (INF) / ventricular volume (VV) assuming a standard deviation (SD) of 10%, a 24% increase in MSI assuming a SD of 20% and a 39% reduction in Troponin area under the curve (AUC) with an SD of 60%. Equal variance was assumed among groups with an unbalanced allocation of patients to placebo (n = 20) and overall FDY-5301 treatment groups (n = 60).

10 DEFINITION OF ANALYSIS POPULATIONS

The **Intent-to-treat (ITT)** population will include patients who gave assent, full consent, abbreviated consent or waived consent and were randomized. This is the "full analysis set" of patients. Patients are included in the ITT population according to the treatment assigned.

The **Safety Population** will consist of all patients who received at least 1 dose of study drug (FDY-5301 or Placebo) and have at least 1 postdose safety assessment.

The **Per Protocol (PP)** population will be a subset of the ITT population and will include patients who gave informed assent/consent, were randomized, received any amount of study drug, underwent PCI, and underwent magnetic resonance imaging (MRI) at 72 ±24 hours and 3 months.

The **PK Population** will consist of all subjects dosed with FDY-5301 and have at least 1 quantifiable postdose PK concentration.

The **PK/PP Population** will consist of all subjects who satisfy the criteria for both the PK and PP 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 patients are assigned to analysis populations. Details of patient assignment to the analysis populations will be listed.

11   STATISTICAL METHODOLOGY

11.1   General

Data listings will be provided for the ITT Population. Summary statistics and statistical analyses will be performed for patients included in the relevant analysis populations.

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: AUCs and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data (i.e. ST-segment resolution and persistent arrhythmias), frequency counts, percentages and odds ratios will be presented, where applicable. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4 or higher.

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 2.1.2 will be utilized to ensure compliance with CDISC standards.

11.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to dosing, including repeat vital signs and unscheduled (clinical laboratory parameters) readings (see Section 11.1.2 for definitions of repeat and unscheduled readings).

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

11.1.2 Repeat and Unscheduled Readings

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.

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 11.1.1).

11.2   Demographics, Patient Disposition, and Baseline Characteristic

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarized and listed. Patient disposition will be summarized and listed.

Selected details from the primary PCI procedure will be summarized and all data will be listed.

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment group, respectively. This data will also be listed.

Important and non-important protocol deviations and the patient assignment to analysis populations will be listed.

11.3   Previous and Concomitant Medications

Any medication which started and ended prior to the start of study drug dosing will be considered as a previous medication. Concomitant medications are medications that are present before the study drug dosing but which were either stopped after the study drug dosing, or ongoing during study and medications that were started on or after the study drug administration.

The previous and concomitant medications will be summarized by preferred term and World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes for each treatment group. Primary PCI medications will not be coded or summarized.

All previous and concomitant medications (including primary PCI medications) will be listed.

11.4   Safety and Efficacy Assessment

All analyses under this section will be performed using the ITT population and also repeated with the PP population.

11.4.1 Primary Analysis (Safety)

Incidence Rate of Events

The primary outcome for this study will be the combined number and incidence rate of several arrhythmias of interest for 14 days post-study drug. The combined number of arrhythmic events in each treatment group will be calculated along with the arrhythmia incidence rate defined as the number of arrhythmia events of interest divided by the total person-time within each treatment group (or the overall FDY-5301 group), expressed as a percentage. The summarization will be presented by 2 separate periods within the 14-day monitoring duration, and also as overall. Period 1 will be the first 48 hours since the start of PCI and period 2 will be the remaining time of 14-day monitoring duration.

The same summarization method will be repeated after stratification of baseline TIMI flow (grade 1 and lower combined, or, grade 2 and 3 combined) and infarct type (anterior or other).

Person-time is an estimate of the time-at-risk in hours for all patients who contributed to the analysis population. The total person-time is calculated as the sum of recording time across patients during the 14 day monitoring period, within each treatment group (or the overall FDY-5301 group). The unit for person-time in this study is person-hours.

The number of arrhythmias of interest and its incidence rates will be summarized by treatment group and the overall FDY-5301 group.

The incidence rate ratio of each active treatment group (and overall) against the placebo group will be calculated.

As an exploratory sub-analysis, the summarization for the number of events and incidence rates will be repeated separately for each arrhythmia category as outlined in Section 6.1 and also separately for non-serious arrhythmias (ie, any arrhythmias which do not meet the criteria as outlined in Section 6.1).

The arrhythmia incidence rates (ie, arrhythmias per person-time) for each arrhythmia type will be summarized by treatment groups in hourly intervals. The intervals may be altered upon reviewing the actual data. Arrhythmia rates by time interval may also be presented in a graphical format.

Occurrence of reperfusion arrhythmias collected prior to use of the continuous rhythm monitoring device will be summarized according to categories as defined in the CRF.

Relationship between each arrhythmia type occurred within 48 hours of the start of PCI procedure and all-cause mortality may be evaluated depending on data availability.

Time-to-Last-Event

The time-to-last-event is defined as the duration between the start time of PCI and the last occurrence of the arrhythmia event. The time-to-event will be censored for a subject if a subject does not experience any arrhythmias of interest before the end of the 14-day monitoring period or the date of early termination from the study. The censoring time will be at the last available time of arrhythmia monitoring.

Median and first and third quartiles of the time-to-last-event will be summarized for each treatment group and the overall FDY-5301 group for each arrhythmia of interest (and combined).

Kaplan-Meier curves will be presented by treatment, baseline TIMI flow, and infarct type for each arrhythmia of interest and also repeated separately for each arrhythmia category.

Time-to-Patch-Application

The duration between the start of PCI to the application of the patch will be derived and summarized by treatment group.

11.4.2 Secondary Efficacy Analysis

11.4.2.1 Infarct Size Parameters from CMR

INF/VV, MSI, and INF will be assessed by CMR at 72 ±24 hours post-study drug and 3 months post-study drug. Summary statistics for the observed values along with changes from baseline will be produced for each treatment group and the overall FDY-5301 group for each parameter. The baseline is defined as the measurement taken at the 72 hour timepoint.

For the changes from baseline for each of these parameters, a single pairwise comparison will be performed to analyze the results between all three FDY-5301 groups (overall) and placebo at both the 3 months post-study drug timepoints. An unpaired Student's T-test will be used for the pairwise comparison if the data are normally distributed and a Mann-Whitney rank test will be used for nonparametric data. Normality will be assessed based on the Shapiro-Wilk test at the 5% level. If the unpaired Student's T-test was selected, the difference in means and its 95% confidence interval will be produced.

Each treatment group will also be tested using a one-way analysis of variance (ANOVA) to obtain a common variance followed by a Dunnett's post-test to separately compare each FDY-5301 dose group to placebo.

The same summarization method and statistical analyses will be repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

The changes from baseline in infarct size parameters may be compared between treatment groups in the form of a frequency table as necessary. The definition for these changes from baseline categories will be determined at a later stage based on the actual data.

11.4.2.2 Proportion of Patients with ST-segment Resolution at 4 hours Post-study Drug

12-lead ECGs will be used to obtain baseline ST-segment elevation prior to treatment in order to evaluate ST-segment resolution 4 hours post-study drug.

ST-segment resolution will be defined as a reduction of the ST-segment elevation by 50% when compared to the baseline. Evaluation of the percentage of ST-segment resolution will be undertaken on the single worst ECG lead (defined as the lead with the maximal ST-segment elevation). Baseline is defined as the maximal ST-segment elevation obtained at Day 1 screening. Results will be categorized as either resolved or non-resolved.

The number of patients with ST-segment resolution will be tabulated by treatment group. Odds ratios will be calculated for each FDY-5301 treatment group (and overall) against the placebo group, along with its 95% confidence interval.

The same summarization method and statistical analyses will be repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

Clinician's ECG interpretation collected from the eCRFs will be listed.

11.4.2.3 Persistent Arrhythmias at 30 Days and 3 Months

12-lead ECGs will be used to confirm any persistent arrhythmias at 30 days and 3 months post-study drug.

Assessments of persistent arrhythmias will be listed and the number of subjects with persistent arrhythmias will be tabulated by treatment group at 30 days and 3 months. Odds ratio will be calculated for each FDY-5301 treatment group against the placebo group, along with its 95% confidence interval.

The same summarization method and statistical analyses will be repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

11.4.2.4 Measures of Cardiac Function by CMR

The EDV, ESV, FS and EF will be assessed at 72 ±24 hours post-study drug and 3 months post-study drug.

Summary statistics will be produced for the observed values along with changes from baseline by each treatment group and the overall FDY-5301 group for each parameter. The baseline is defined as the measurement taken at the 72 hour timepoint.

For the changes from baseline for each of these parameters, a single pairwise comparison will be performed to analyze the results between all three FDY-5301 groups (overall) and placebo. An unpaired Student's T-test will be used for the pairwise comparison if the data are normally

distributed and a Mann-Whitney rank test will be used for nonparametric data. Normality will be assessed based on the Shapiro-Wilk test at the 5% level. If the unpaired Student's T-test was selected, the difference in means and its 95% confidence interval will be produced.

The parameters from each group will then be tested using a one-way ANOVA to obtain a common variance followed by a Dunnett's post-test to separately compare each FDY-5301 dose group to placebo.

The same summarization method and statistical analyses will be repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

11.4.2.5 Serum Levels of Troponin

The troponin AUC_{0-48} will be derived from the serum levels of troponin collected at the following timepoints: Predose, 4, 12, 24 and 48 hours post-study drug. AUC_{0-48} will be calculated using the linear trapezoidal method. Where possible, the derivation will be carried out using actual post-dose times recorded. If actual times are missing, nominal times may be used with sponsor approval.

Summary statistics (also including geometric means and geometric coefficient of variation [CV] %) for the serum levels will be produced by each treatment group and the combined FDY-5301 group for the derived AUC_{0-48}. The summary statistics for troponin AUC_{0-48} will be presented in a similar way.

The derived AUC_{0-48} will be logarithmically transformed, and an unpaired Student's T-test will be used analyze its differences between all three FDY-5301 groups (overall) and placebo.

The logarithmically transformed AUC_{0-48} from each group will then be tested using a one-way ANOVA to obtain a common variance followed by a Dunnett's post-test to separately compare each FDY-5301 dose group to placebo.

The arithmetic least squares means of the treatment differences will be back-transformed to provide the geometric means and its 95% confidence interval.

The same summarization and statistical analyses will be repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

11.4.2.6 Plasma Biomarkers of Cardiac Injury, Inflammation, and Remodeling

The plasma biomarker C_{max} and AUC_{0-48} will be derived from the plasma biomarker levels collected at the following timepoints: Predose, 1, 4, 12, 24 and 48 hours post-study drug. AUC_{0-48} will be calculated using the linear trapezoidal method. Where possible, the derivation will be carried out using actual post-dose times recorded. If actual times are missing, nominal times may be used with sponsor approval. Maximum deviation defined as the largest magnitude shift (or absolute change) from baseline will be derived.

Summary statistics (also including geometric means and geometric CV%) for each plasma biomarker concentration will be produced by each treatment group and the overall FDY-5301 group for the values and its changes from baseline. The baseline is defined as the last actual value obtained prior to study drug infusion.

For each of these plasma biomarker concentrations, a single pairwise comparison will be performed by timepoint to analyze change from baseline value between all three FDY-5301 groups (overall) and placebo. An unpaired Student's T-test will be used for the pairwise comparison if the data are normally distributed and a Mann-Whitney rank test will be used for nonparametric data. Normality will be assessed based on the Shapiro-Wilk test at the 5% level.

Each group will then be tested using a one-way ANOVA to obtain a common variance followed by a Dunnett's post-test to separately compare each FDY-5301 dose group to placebo.

The logarithmically transformed C_{max}, AUC_{0-48} and maximum deviation from each group will be tested using a one-way ANOVA to obtain a common variance followed by a Dunnett's post-test to separately compare each FDY-5301 dose group to placebo.

The arithmetic least squares means of the treatment differences will be back-transformed to provide the geometric means and its 95% confidence interval.

The same summarization and statistical analyses for plasma biomarker concentrations and parameters will be repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

11.4.3 Exploratory Analysis (Safety)

Incidence Rate of New Onset Atrial Fibrillation

The exploratory outcome for this study will be the combined number and incidence rate of new onset atrial fibrillation for 14 days post-study drug. The combined number of events in each treatment group will be calculated along with incidence rate defined as the number of events divided by the total person-time within each treatment group (or the overall FDY-5301 group), expressed as a percentage.

The number of new onset atrial fibrillation and new onset atrial fibrillation incidence rates will be summarized by treatment group and the overall FDY-5301 group.

The incidence rate ratio of each active treatment group (and overall) against the placebo group will be calculated.

The summarization will be presented by 2 separate periods within the 14-day monitoring duration, and also as overall. Period 1 will be the first 48 hours since the start of PCI procedure and period 2 will be the remaining time of 14-day monitoring duration.

11.5 Safety and Tolerability Assessments

All safety analyses will be performed with the safety population.

11.5.1 Adverse Events

The study specifically recruits STEMI patients; therefore the myocardial infarction (MI) itself will not be characterized as an AE. However, complications arising as a consequence of the MI, for example, an emergent or worsening heart failure, death, or arrhythmias will be specifically documented as adverse events in the CRFs.

A baseline sign and symptom is defined as an AE that starts after the patient 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 summarized by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of patients experiencing a TEAE, and the percentage of patients experiencing a TEAE) of TEAEs and serious TEAEs will be summarized by treatment, and by MedDRA 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 drug (those that have a relationship of probable or possible). A subset of serious adverse events and adverse events which are cardiac related, including the development of heart failure, will also be presented as summary tables. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries. Any life-threatening, severe or serious AEs will be listed.

Onset times postdose are calculated from the start of study drug infusion.

11.5.2 Clinical Laboratory Parameters

Clinical chemistry (including thyroid function tests) and hematology data will be summarized by treatment group. Changes from baseline will be calculated. Shift tables from baseline will be presented. In addition, all clinical chemistry and hematology data outside the clinical reference ranges will be listed by parameter and treatment.

Values for any clinical chemistry and hematology values outside the clinical reference ranges will be flagged on the individual patient data listings.

11.5.3 Vital Signs

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

The vital signs data will be summarized by treatment group, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by treatment. Repeat and unscheduled readings will be handled as defined in Section 11.1.2.

11.5.4 Incidence of Mortality

The incidences of all-cause and cardiac mortality out to 6 months post PCI will be listed and tabulated by treatment group.

11.5.5 Other Safety Assessments

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

11.5.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11.6   Pharmacokinetic Assessment

11.6.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from plasma iodide concentrations using non-compartmental methods performed using Phoenix WinNonlin (Version 6.4 or higher):

Parameter	Definition
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last observed quantifiable concentration (T_{last}), calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
AUC_{inf}	area under the concentration-time curve extrapolated to infinity calculated using the following equation: $AUC_{inf} = AUC_{last} + C_t/Kel$ where C_t is the last observed quantifiable concentration and Kel is the terminal elimination rate constant.
C_{max}	maximal observed plasma concentration
T_{max}	time when maximal concentration is achieved
T_{last}	time of last quantifiable concentration
Kel	apparent terminal elimination rate constant
$T_{1/2}$	apparent terminal elimination half-life, calculated as natural log (ln)(2)/Kel
CL	total body clearance
V_z	volume of distribution during the terminal elimination phase
V_{ss}	volume of distribution at steady-state

Additional PK parameters may be determined where appropriate. If the IV bolus model is used (refer to last bullet point in Section 11.6.4), then C_0 (back-extrapolated concentration at time zero) may be calculated by excluding the observed predose concentration value and then using a log-linear regression of the first 2 postdose data points to back-extrapolate to the concentration at time 0.

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 approval.

Concentrations will be 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.

The dose level of FDY-5301 (sodium iodide) will be converted to its free base equivalent for PK analysis if the analytical laboratory reports the free base concentration.

C_{max}, T_{max}, and T_{last} 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.

11.6.2 Criteria for Handling Concentrations Below the Limit of Quantification in

Pharmacokinetic Analysis

- Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows;

    o 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.

    o 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.

    o If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

    o If a predose concentration is missing, it may be set to zero with sponsor approval.

11.6.3 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

11.6.3.1 Number of Data Points

- At least three data points will be included in the regression analysis and preferably should not include C_{max}.

11.6.3.2 Goodness of Fit

- When assessing terminal elimination phases, the adjusted coefficient for the determination of exponential fit (R^2 adjusted) will be used as a measure of the goodness of fit of the data points to the determined line.

- Kel and Kel-based parameters will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

11.6.3.3 Period of Estimation

- Apparent terminal elimination half-life will be estimated over a time period of at least two half-lives, where possible.

- Where $T_{1/2}$ is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value should be discussed in the study report.

11.6.4 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

- For any partial AUC determination, nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- AUC_{inf} values where the percentage extrapolation is less than 20% will be reported. AUC_{inf} values where the percentage extrapolation is between 20 to 30% will be reported, flagged, and included in the descriptive statistics, while AUC_{inf} values where the percentage extrapolation is greater than 30% will be reported and flagged, but excluded from descriptive statistics.

- If an IV bolus model is used, and if the combined area of back-extrapolated and infinity-extrapolated is >30%, AUC_{inf} may not be reported or a different model may be used (such as the infusion model), at the discretion of the Pharmacokineticist.

11.6.5 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.

11.6.6 Presentation of Pharmacokinetic Data

11.6.6.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

- The following rules will be applied if there are values that BLQ or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.

    o For the calculation of summary statistics, BLQ values will be set to zero.

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

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

    o If there are less than 3 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.

o 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.

o If the value of the arithmetic mean or median is BLQ, it will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.

11.6.6.2 Presentation of 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 values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last is C_{max}.

11.6.7 Pharmacokinetic Statistical Methodology

All PK analyses will be performed with the PK population.

All reportable plasma iodide concentration data and derived PK parameters will be summarized by treatment and listed.

Plasma concentrations and derived PK parameters will be summarized in terms of N, arithmetic mean, SD, median, minimum, maximum, geometric mean and geometric CV%. For the PK parameter T_{max} and T_{last}, the descriptive statistics will not include geometric mean, and geometric CV%. Individual figures will also be presented using actual sampling times.

There are no formal inferential statistical analyses planned.

11.6.8 Pharmacokinetic/Efficacy Analysis

A scatterplot will be produced to evaluate potential correlations between the Iodide plasma AUC_{inf} and INF/VV at 3 months post-study drug.

12 INTERIM ANALYSES

After the 14 day follow-up visit to the clinic, all patients' data will be collected and analyzed for:

- Safety (14-day arrhythmias)

After the 3 month follow up visit, analysis of the following will occur:

- Early efficacy outcomes including MSI, INF/VV, INF

- Serum troponin AUC_{0-48} hours post-study drug

- ST-segment resolution by 4 hours post-study drug

- Cardiac function including EDV, ESV, FS and EF

All remaining assessments will be analyzed at the conclusion of the study.

13   CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

For the analysis of arrhythmias of interest, a person-time adjustment will be applied to account for potential missing data during the 14-day monitoring period, due to possible unforeseen reasons such as patient withdrawal, device failure or death. The incidence rate for each treatment group (and overall FDY-5301) will be calculated as the number of events divided by the total person-time of monitoring within each treatment group. The incidence rate ratios of each treatment group (and overall FDY-5301) versus the placebo will be derived.

Scope of the interim analyses has been updated.

Overall summary for primary and exploratory safety and efficacy endpoints will be summarized by stratification of TIMI flow grade and infarct location

14   DATA PRESENTATION

14.1   Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients 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."

15   REFERENCES

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

1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, safety, efficacy, 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:
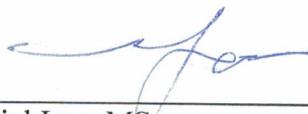
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Gabriel Lau, MSc
Statistician

10 APR 2018
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Date

_____
Sarah Thorn, BS
Pharmacokineticist

_____
Date

Sponsor approval:

12 April 2018
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Lori Siegel, MPH
Clinical Project Manager

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Date

_____
Simon Tulloch, BM, BCh
Chief Medical Officer

_____
Date