FARADAY PHARMACEUTICALS, INC.

FDY-5301-201-US

Study Title:	**A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Intravenous FDY-5301 in Acute Myocardial Infarction**
Study Drug:	**FDY-5301**
Protocol Number:	**FDY-5301-201-US**
Drug Development Phase:	**2A**
Sponsor:	**Faraday Pharmaceuticals, Inc.** **1616 Eastlake Ave E, Suite 560** **Seattle, WA 98102** **(206) 492-5310**
Protocol Version/Date	**Version 2 / May 21, 2018**

Confidentiality Statement

This document contains confidential information of Faraday Pharmaceuticals Inc. that must not be disclosed to anyone other than the recipient study staff and members of the study site. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Faraday Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Intravenous FDY-5301 in Acute Myocardial Infarction" dated 09 May 2018 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice, the ethical principles stated in the latest version of the Declaration of Helsinki, and the applicable local and international regulations, whichever provide the greater protection of the individual.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Faraday Pharmaceuticals, Inc.

_____

Signature

_____ _____

Principal Investigator ***Date (DD Month YYYY)***

SPONSOR STATEMENT

This study protocol was subject to critical review and has been approved by the following sponsor representative.

Signature

Simon Tulloch — 21 May 2018

Chief Medical Officer — ***Date (DD Month YYYY)***

1 SYNOPSIS

Name of Sponsor/Company:	Faraday Pharmaceuticals, Inc. 1616 Eastlake Ave E, Suite 560 Seattle, WA 98102
Name of Investigational Product:	FDY-5301
Name of Active Ingredient:	Sodium Iodide (NaI)
Title of Study:	A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Intravenous FDY-5301 in Acute Myocardial Infarction
Principal Investigator:	TBD
Sub-Investigator(s):	TBD
Estimated date first patient enrolled:	3Q, 2017
Estimated date last patient completed:	2Q, 2018
Phase of development:	Phase 2A safety and efficacy study
Purpose:	To evaluate the safety, efficacy and pharmacokinetics (PK) of 3 dose levels of FDY-5301 compared to placebo in patients presenting with an acute ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).
Primary Outcome:	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. These arrhythmias include ventricular fibrillation, sustained and non-sustained ventricular tachycardia and high degree AV block. Continuous cardiac monitoring will occur for 14 days post PCI by means of

	wearable patch devices.
Secondary Outcomes:	Infarct size parameters will be assessed by cardiac magnetic resonance (CMR) at 72 +/-24 hours post-study drug and 3 months post-study drug; the following will be compared between groups; infarct size as a proportion of ventricular volume (INF/VV), myocardial salvage index (MSI) and absolute myocardial infarction size (INF). The proportion of patients with ST-segment resolution at 4 hours post-study drug Serum levels of troponin calculated as AUC over 48 hours post treatment Persistent arrhythmias at 30 days and 3 months Measures of cardiac function by CMR including end-diastolic volume (EDV), end-systolic volume (ESV), fractional shortening (FS) and ejection fraction (EF) at discharge and 3 months Biomarkers of cardiac injury, inflammation and remodeling out to 3 months of follow up Cardiac related adverse events including the development of heart failure out to 3 months of follow up Incidence of all cause and cardiac mortality out to 6 months of follow up
Additional Safety and tolerability:	Physical examination including vital signs, clinical chemistry, hematology and thyroid function tests will be monitored. Adverse Events (AEs) and Serious Adverse Events (SAEs) will be recorded. 12 lead ECGs will be evaluated at intervals and post baseline.
Pharmacokinetics:	Plasma iodide samples will be taken to estimate C_{max}, AUC, T_{max} and $T_{1/2}$.

Methodology:	This is a Phase 2A, randomized, double-blind, placebo-controlled, multi-center study that will evaluate safety, efficacy and PK of FDY-5301 in subjects with acute STEMI undergoing PCI. Up to 160 patients will be randomized to obtain a final sample size of 80 evaluable patients. By evaluable, we mean that a patient must have a complete dataset with regard to measures of arrhythmia data and infarct size. Subjects 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 ECG findings, within an hour prior to myocardial reperfusion. All subjects will have an early CMR, 14 days of arrhythmia monitoring, and will be followed up for safety and efficacy for up to 6 months. Subjects will be monitored in hospital, and return for clinic visits at day 14, day 30 and 3 months post PCI. At the clinic visits, subjects will undergo evaluation to include measurement of laboratory safety parameters, adverse events, ECG. At the 3 month clinic visit, infarct size will also be assessed by CMR, and the presence of any persistent arrhythmias will be assessed by the investigator using an ECG rhythm strip. Follow up by phone to determine all cause and cardiac mortality status will occur at 6 months post-study drug. If the subject is unavailable then mortality status will be obtained from physician/investigator records.
Number of patients:	Up to 160 patients
Diagnosis and main criteria for inclusion:	1. 18-80 year old male subjects 2. 18 to 80 year old female subjects who are not of child-bearing potential 3. Accepted for Primary PCI with diagnosis of first STEMI, based on clinical and ECG criteria (ST-elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 millivolt (mV) in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads) within 12 hours of symptom onset 4. Written informed consent prior to study participation (either by the subject or a

	legally authorized representative of the subject)
Exclusion Criteria:	1. Previous myocardial infarction 2. Left bundle branch block (LBBB) 3. Previous coronary artery bypass graft surgery (CABG) 4. Major hemodynamic instability or uncontrolled ventricular arrhythmias 5. Known contraindication to CMR (e.g. pacemaker) 6. Patients with known thyroid disease, or known allergy to iodide 7. Subjects with past or current renal impairment requiring dialysis 8. Pregnant or females of childbearing potential 9. Body weight > 120 kg or Body Mass Index (BMI) > 35 kg/m2 10. Use of investigational drugs or devices within 30 days prior to enrollment into the study 11. Life expectancy of less than 1 year due to non-cardiac pathology 12. Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study
Investigational product, dosage and mode of administration:	FDY-5301 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg or placebo will be administered intravenously (IV) by bolus injection between an hour and 5 minutes prior to coronary artery reperfusion.
Duration of treatment:	Treatment is a single IV bolus administration of study drug. Each subject will be involved up to 6 months from screening until study exit.
Reference therapy, dosage and mode of administration:	Placebo (normal saline for injection). Placebo will be indistinguishable from FDY-5301.
Statistical methods:	The primary outcome for this study will be the combined number and incidence rate of

several arrhythmias of interest that occur in each group over a 14 day period post-study drug. These arrhythmias including ventricular fibrillation, sustained ventricular tachycardia (≥125 BPM, ≥ 30 seconds), non-sustained ventricular tachycardia (≥ 125 BPM, ≥ 16 beats, < 30 seconds) and high degree AV block (2nd or 3rd degree, ≥ 8 beats) were chosen because they are significant prognostic indicators of depressed left ventricular ejection fraction and cardiac death [1]. The combined number of arrhythmic events in each group will be calculated along with the arrhythmia incidence rate defined as the percentage of patients in each group experiencing at least one of the defined arrhythmias of interest.

An exploratory sub-analysis will be conducted to determine the number and incidence rate of each separate arrhythmia type per dose group.

Little data exists on the incidence of arrhythmias that occur over an extended period of time following AMI and monitoring strategies for this type of assessment have not been optimized in a clinical trial setting. The primary goal of our study is to characterize the occurrence of arrhythmias in this patient population for 14 days post-AMI and to determine the feasibility of using ambulatory patch ECG monitors to capture this data. These data should be regarded as exploratory with the objective of identifying a meaningful clinical end point that can be easily measured in future, pivotal studies that are adequately powered to detect differences across treatment groups.

As this is the first clinical study in patients, safety is the primary focus. For this reason, the goal is to enroll a limited number of patients to FDY-5301 while still powering the study to detect significant differences in efficacy measures across groups. Estimating a drop-out rate of 50%, we will need to enroll up to 160 patients in order to obtain a final total sample size of 80 patients. A final sample size of 80 patients will provide 80% power to detect a 37% reduction in INF/VV assuming an SD of 10%, a 24% increase in MSI assuming an SD of 20% and a 39% reduction in Troponin AUC with an SD of 60%. Equal variance was assumed among groups with an unbalanced allocation of patients to placebo (n=20) and combined FDY-5301 treatment groups (n=60).

Exploratory efficacy outcomes will include:

Between group comparisons of infarct size as a proportion of ventricular volume (INF/VV), the myocardial salvage index (MSI), and absolute MI size (INF) at 72 +/- 24 hours and 3 months post PCI as measured by CMR will be performed.

The proportion of patients with ST-segment resolution at 4 hours post study drug.

Serum levels of troponin calculated as AUC 0-48 hours post study drug.

Cardiac-related adverse events including the development of heart failure out to 3 months of follow up

The incidence of all cause and cardiac mortality out to 6 months post PCI.

In addition to the measurement of safety and efficacy parameters in this study, serum biomarker levels of cardiac injury, inflammation and remodeling will also be assessed.

After the 14 day follow up visit to the clinic, analysis of all subjects' data will be collected and analyzed for safety (arrhythmias) and early efficacy outcomes.

After the 3 month follow up visit, analysis of efficacy outcomes including final MSI, INF/VV, INF parameters and cardiac function including EDV, ESV, FS and EF will be analyzed. All remaining assessments will be analyzed at the conclusion of the study.

For PK analysis, C_{max}, AUC, T_{max} and $T_{1/2}$ will be calculated for each dose based on plasma iodide levels.

Document History

Protocol Number: **FDY-5301-201**

Original Protocol Date: **August 30, 2017**

Amendment Number	Amendment Date	Explanation of Changes

Table 1: Emergency Contact Information

Clinical Research Organization (CRO)

Role in Study	Name	Address and Telephone Number
Study Project Leader	TBD	
Medical Monitor	TBD	

Sponsor Representative

Role in Study	Name	Address and Telephone Number
Medical Monitor	TBD	

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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Explanation
ACT	activated clotting time
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AST	aspartate transaminase
AUC	area under (concentration-time) curve
BMI	body mass index
BP	blood pressure
CL	Clearance
C_{max}	maximal drug concentration
CMR	cardiac magnetic resonance
CRF	case report form
DLT	dose limiting toxicity
ECG	Electrocardiogram
EDV	end diastolic volume
ESV	end systolic volume
EF	ejection fraction
FS	fractional shortening
GCP	good clinical practice
GLP	good laboratory practice

Abbreviation or Specialist Term	Explanation
GGT	gamma-glutamyl transferase
HR	heart rate
IB	investigators brochure
ICH	international conference on harmonization
INF	infarct size
IRB	institutional review board
IV	Intravenous
Kg	Kilogram
LAR	legally appointed representative
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
MI	myocardial infarction
mL	Milliliters
MSI	myocardial salvage index
NOAEL	no adverse effect level
OOR	out of range
PCI	percutaneous coronary intervention
PCV	packed cell volume
PI	principal investigator
PK	Pharmacokinetic
RBC	red blood cell count

Abbreviation or Specialist Term	Explanation
RR	respiratory rate
SAE	serious adverse event
$T_{1/2}$	elimination half-life
T_{max}	time to maximal drug concentration
V	volume of distribution
WCC	white cell count

3 INTRODUCTION

3.1 Disease

The first line of therapy for STEMI includes coronary artery reperfusion by mechanical means (angioplasty). While clearly effective, it does not address the issue of "reperfusion injury", a secondary damage that develops due to the revascularization of the previously ischemic myocardial tissue. Even though angioplasty has dramatically improved the survival rate, the goal of developing FDY-5301 in AMI is to reduce infarct size, and consequently improve short and longer-term outcomes after AMI/reperfusion.

3.2 FDY-5301 Background

FDY-5301 product (herein after referred to as FDY-5301) is sodium iodide formulated as an isotonic solution in a single use vial for intravenous administration. The solution has a pH between 7.0 and 9.5. A monograph for sodium iodide is listed in the current United States Pharmacopoeia (USP). The chemical formula of sodium iodide is NaI.

The route of administration is by intravenous (IV) injection.

As discussed in the Investigators Brochure (IB), the nonclinical safety assessment of FDY-5301 includes pilot and Good Laboratory Practice (GLP) 7 and 14 day IV repeat dose toxicity studies, pharmacokinetic studies, local tolerability studies, a series of in vitro and in vivo safety pharmacology, in vitro hemocompatibility, in vitro cytochrome P450 inhibition, in vitro protein binding, and genotoxicity studies conducted in accordance with International Conference on Harmonization (ICH) guidelines.

An IV bolus single dose toxicity study in rats showed that FDY-5301 was associated with no mortality in animals receiving bolus injections of up to 1000 mg/kg. Adverse clinical signs were not observed in either gender.

In rats, no signs of toxicity were observed at doses up to 74 mg/kg given daily IV for 14 days. In beagle dogs the NOAEL was established at 20 mg/kg for 7 days dosing. The observed DLT at 40 mg/kg was reversible gastro-intestinal inflammation.

Safety pharmacology studies included an in vitro hERG K^+ ion channel assay, a CNS safety pharmacology study (general signs and behavior) in rats, a pulmonary safety pharmacology study in rats, and a cardiovascular safety pharmacology study in dogs. Overall, the results of these studies show that at the dosing regimen and at expected systemic exposures of FDY-5301 to be achieved in humans, no adverse effects are anticipated to occur in any of the major organ systems tested.

FDY-5301 was found not to be mutagenic in the bacterial reverse mutation assay.

Other studies with FDY-5301 show that the formulation to be used for clinical trials is not expected to cause local perivenous irritation. In addition, it does not exhibit protein binding nor does it inhibit cytochrome P450 enzymatic activity. FDY-5301 was also shown to be compatible with human, dog, and rat serum, plasma, and whole blood.

As well as the extensive experience and known safety of orally administered iodide, it has been used intravenously in humans to manage thyrotoxic crisis.

Faraday has conducted a phase 1 single ascending dose study in healthy volunteer subjects at intravenous doses of up to 10 mg/kg. No significant adverse events were detected, including biochemical measures of thyroid function. The anticipated therapeutic dose is likely in the range of 0.5 to 2.0 mg/kg based on nonclinical studies and human PK data.

3.3 Rationale

Preclinical pharmacology data to date show that FDY-5301 when administered in conjunction with the revascularization of previously ischemic myocardium significantly reduces infarct size, improves myocardial function and coronary perfusion, reduces neutrophil infiltration and down-regulates the inflammatory response in the reperfused myocardial tissue. FDY-5301 may reduce myocardial reperfusion injury in patients with AMI undergoing revascularization, and consequently, reduce infarct size. No clinical trials in AMI patients have yet been conducted with FDY-5301. The anticipated human effective dose based on preclinical data is from 0.5 to 2.0 mg/kg. The study outlined herein is designed to assess the safety, efficacy and PK of FDY-5301 in patients with first STEMI about to undergo PCI.

4 TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety, efficacy, and pharmacokinetics (PK) of three dose levels of FDY-5301 compared to placebo in STEMI patients undergoing PCI.

4.1 Primary Outcome

The primary outcome for this study will be the combined number and incidence rate of several arrhythmias of interest that occur in each group over a 14 day period post-study drug. These arrhythmias including ventricular fibrillation, sustained ventricular tachycardia (≥125 BPM, ≥ 30 seconds), non-sustained ventricular tachycardia (≥ 125 BPM, ≥ 16 beats, < 30 seconds) and high degree AV block (2^{nd} or 3^{rd} degree, ≥ 8 beats) were chosen because they are significant prognostic indicators of depressed left ventricular ejection fraction and cardiac death [1]. The combined number of arrhythmic events in each group will be calculated along with the arrhythmia incidence rate defined as the percentage of patients in each group experiencing at least one of the defined arrhythmias of interest.

An exploratory sub-analysis will be conducted to determine the number and incidence rate of each separate arrhythmia type per dose group.

Continuous cardiac monitoring will occur for 14 days post PCI by means of wearable patch devices.

4.2 Secondary Outcomes

Infarct size parameters will be assessed by CMR at 72 +/- 24 hours and 3 months; the following will be compared between groups; infarct size as a proportion of ventricular volume (INF/VV), myocardial salvage index (MSI) and absolute MI size.

- The proportion of patients with ST-segment resolution at 4 hours post study drug
- Serum levels of troponin calculated as AUC 0-48 hours post-study drug
- Persistent arrhythmias at 30 days and 3 months
- Measures of cardiac function by CMR including end-diastolic volume (EDV), end-systolic volume (ESV), fractional shortening (FS) and ejection fraction (EF).
- Serum biomarkers of cardiac injury, inflammation and remodeling
- Cardiac-related adverse events including the development of heart failure out to 3 months of follow up
- 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.

Safety and Tolerability:

Physical examination including vital signs, laboratory measures to include clinical chemistry, hematology and thyroid function tests will be performed. Adverse Events (AEs) and Serious Adverse Events (SAEs) will be recorded.

12 lead ECGs will be performed at intervals at and post baseline.

Pharmacokinetics:

Plasma iodide levels will be measured in each patient. The concentration-time profile of plasma iodide will be derived for each of the groups. The pharmacokinetics of iodide will be described as area under the concentration versus time curve (AUC), the maximal concentration (C_{max}) and the time (T_{max}) when the maximal concentration is achieved. The terminal half-life ($T_{1/2}$), the total body clearance (CL), and the volume of distribution (V) will also be derived.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan: Description

This is a Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Intravenous FDY-5301 in Acute Myocardial Infarction (AMI).

Study subjects will be recruited at each investigational site (or referred to the investigative site from another institution) for treatment of first STEMI. Subjects will be screened and written informed consent will be obtained prior to initiation of any study related procedures in those subjects who meet the inclusion and exclusion criteria for the study.

Up to 160 patients will be randomized to receive either FDY-5301 at doses of 0.5 mg/kg, 1.0mg/kg, 2.0mg/kg or placebo.

STEMI diagnosis will be made based on clinical and ECG findings including: subjects presenting with ≥ 30 minutes of ischemic chest pain, within 12 hours of symptom onset, and have persistent ST-segment elevation of ≥ 2 mm in at least 2 contiguous leads in ECG.

Study drug administration will occur by bolus injection at any time between an hour and 5 minutes prior to coronary reperfusion.

All patients who receive study drug and have PCI will be followed up for safety and efficacy for 6 months post-study drug infusion. Subjects who do not undergo angioplasty for any reason who received study drug will be followed up for safety, but will be replaced with a new subject.

5.2 Number of Centers/Subjects

This study will be conducted at up to 20 centers in the USA and Europe. European sites are not using this version of the protocol and will not be submitted to the IND. Up to 160 STEMI patients are planned for enrolment in this study to obtain a final sample size of 80 patients.

5.3 Estimated Study Duration

This study is expected to take up to 12 months to complete screening and enrollment for all subjects. Each subject's participation will be up to 6 months from the time of screening to study exit.

5.4 Assignment to Study

Screening numbers will be assigned sequentially at each study site as soon as informed consent has been obtained either by the subject or a legally authorized representative of the subject. Information from patients who are screened and do not meet the study entry criteria will be entered into a screening log. Once assigned, screening numbers for any screening failures, untreated, non-evaluable, or discontinued subjects will not be re-used.

All subjects who satisfy the Inclusion/Exclusion criteria will be randomly allocated to one of four treatment groups (FDY-5301 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, or placebo).

5.5 Schedule of Assessments

For each subject, the study will consist of Screening/Treatment (Day 1), evaluations at Day 2 and Day 3, and follow-up visits at 14 days, 30 days and 3 months, and a telephone call at 6 months (see Figure 1).

5.5.1 Screening (Day 1 – Prior to PCI)

1. Prospective subjects will present to the hospital and will be screened for inclusion in this study if they present with ≥ 30 minutes of ischemic chest pain, will be catheterized within 12 hours of symptom onset, and have persistent ST-segment elevation of ≥ 2 mm in at least 2 contiguous leads in ECG. They will have the purpose of the study and its procedures and risks explained

Subjects, or their legally appointed representative (LAR), must give written informed consent before any screening procedures can be started. During screening the following procedures will be conducted for all subjects if possible to determine study eligibility (some medical history may be gathered after treatment if not an exclusion criterion):

- Inclusion/Exclusion criteria will be documented

- 12-lead ECG for STEMI diagnosis
- Demographics (age, gender, smoking status)
- General medical/surgical history (co-morbidities, duration of symptoms, and prior and present therapies)
- Study specific medical/surgical history and concomitant conditions, especially thyroid disorders
- Prior and current medications taken within two weeks prior to study drug administration
- Physical examination
- Vital signs including: temperature, pulse, respiratory rate, blood pressure
- Height and weight: In the event that the body weight is not available at time of study drug dosing, the subject's last reported weight or estimated weight will be used for study drug dosage calculation.

5.5.2 Treatment Day 1 – in Cardiac Catheterization Lab and Recovery

- Random allocation to study drug (once screening is complete and consent is obtained either from the subject or a legally authorized representative of the subject, randomization must occur to ensure study drug is given by bolus injection between an hour prior to and 5 minutes prior to coronary reperfusion, so as to be complete at least 5 minutes prior to reperfusion)
- Study drug administration
- Vital signs (pulse, respiratory rate, blood pressure) will be recorded every 15 minutes after study drug for an hour, then hourly for another 4 hours. There is a +/- 10 minute window on all vital sign collections
- Blood sampling to assess anticoagulation during the procedure (INR)
- Documentation of peri-procedural arrhythmias by medical staff by 12-lead ECG
- Continuous ECG monitoring will commence post procedure as soon as the 7 day wearable device can be affixed to the patient and up to 14 days post study drug[1]
- Standard 12 lead ECG prior to treatment to obtain baseline ST-segment elevation and again at 4 hours post-study drug to assess ST segment resolution (3 strips at each time point)
- Blood samples for troponin T will be obtained (see time points in Section 12)
- PK blood sampling (see time points in Section 12)
- Blood sample to assess biomarkers of cardiac injury and inflammation (see time points in Section 12)
- Laboratory safety tests (as outlined in Section 12)
- Recording of concomitant medications
- Recording of any AEs
- If study informed consent was given by the subject's legally authorized representative for study enrollment, the subject will be provided with a modified consent once they are stable (after investigational drug treatment and STEMI procedure) and

in the opinion of the investigator capable of providing written consent. This modified informed consent document will cover the subject's agreement to remain in the clinical trial and proceed with all study related procedures and follow-up.

[1] The wearable ECG monitor device should be affixed to the patient as soon as possible post-study drug. This single-use device will need to be removed when the patient undergoes CMR at 72 +/- 24 hours post-study drug. At that time, a new wearable ECG monitor device will need to be affixed to the patient.

5.5.3 Day 2 (24 hours +/- 2 hours post-study drug)

- Physical examination and vital signs (pulse, respiratory rate, blood pressure)
- Laboratory safety tests (as outlined in Section 12)
- Blood samples for troponin T will be obtained (see time points in Section 12)
- PK blood sampling (see time points in Section 12)
- Blood sample to assess biomarkers of cardiac injury and inflammation (see time points in Section 12)
- Recording of any AEs
- Concomitant medications

5.5.4 Day 3 (48 hours +/- 2 hours post-study drug)

- Physical examination and vital signs (pulse, respiratory rate, blood pressure)
- Laboratory safety tests (as outlined in Section 12)
- Blood samples for troponin T will be obtained (see time points in Section 12)
- Blood sample to assess biomarkers of cardiac injury and inflammation (see time points in Section 12)
- Recording of any AEs
- Concomitant meds

5.5.5 First CMR (72 hours +/- 24 hours post-study drug)

- CMR to measure MSI, INF/VV, INF and cardiac function including EDV, ESV, FS and EF. If CMR cannot be completed at the time of discharge, the patient should be encouraged to return for a CMR 48-96 hours post-study drug.
- Physical examination and vital signs (pulse, respiratory rate, blood pressure) (at time of discharge)
- Recording of any AEs (at time of discharge)
- Concomitant medications (at time of discharge)

- Discharge with instructions for continuous ECG device (at time of discharge)[2]

[2] Instructions for the wearable ECG monitoring device will be given prior to discharge. The wearable ECG monitoring devices can collect data for 7 days therefore, a follow up phone call will be conducted 7 days after the wearable ECG monitoring device was first affixed to the patient to ensure compliance with removing the wearable ECG monitoring device and replacing it with another one. Instructions will also be given at that time on retaining the first week's data for return to the clinic at day 14.

5.5.6 Follow-up 14 days (+/- 2 days post drug)

- Physical examination and vital signs (pulse, respiratory rate, blood pressure)
- Body weight (kg)
- Laboratory safety tests (as outlined in Section 12)
- Recovery of wearable ECG devices and recordings
- Recording of any AEs
- Concomitant medications

5.5.7 Follow-up 30 days (+/- 1 week post drug)

- Physical examination and vital signs (pulse, respiratory rate, blood pressure)
- Body weight (kg)
- Laboratory safety tests (as outlined in Section 12)
- 12-lead ECG including rhythm strip to identify persistent arrhythmias
- Recording of any AEs
- Concomitant medications

5.5.8 Follow-up 3 months (+/- 2 weeks post drug)

- CMR to measure MSI, INF/VV, INF and cardiac function including EDV, ESV, FS and EF
- Recording of any AEs
- Concomitant medications
- 12-lead ECG including rhythm strip to identify persistent arrhythmias
- Blood sample for analysis of biomarkers of remodeling

5.5.9 Follow-up 6 months or early termination (+/- 4 weeks post drug)

Telephone interview with the subject (or relative if subject unable to give history) for incidence of all cause and cardiac mortality. If subject is unavailable, then physician/investigator records will be source of mortality documentation if available.

Figure 1: Study Diagram

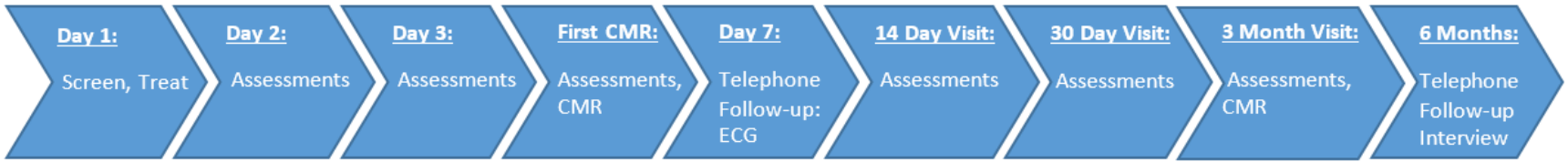

Table 2: Study Design and Schedule of Assessments

Activity	Screening Day 1	Treatment Day 1	Day 2 (24 +/- 2 Hrs)	Day 3 (48 +/- 2 Hrs)	First CMR (72 +/-24 Hrs)	Day 7	14 day (+/- 2 days)	30 day (+/- 1 week)	3 month (+/- 2 weeks)	6 month/Early Termination (+/- 4 weeks)
Inclusion/Exclusion Criteria, IC[14]	X									
Demographics/Medical History	X									
Physical Examination(including Con meds)	X		X	X	X		X	X	X	
Vital Signs, con meds	X	X[10]	X	X	X		X	X	X	
Height and Weight	X									
Safety Laboratory tests		X[3]	X	X			X	X		
Troponin T		X[4]	X	X						
Randomization, study drug		X								
ACT during anticoagulation		X								
Document peri-proc. arrhythmias		X								
Continuous ECG										
Phone call re continuous ECG						X				
12 lead ECG	X	X[11]						X[12]	X[13]	
PK-Iodide levels		X[5]	X	X						
Cardiac Biomarkers		X[6]	X	X					X	
CMR					X[7]				X	
Adverse Events	X	X	X	X	X		X	X	X	

Follow up phone call or review of physician records for all-cause mortality										X
Un-blinded Interim Analysis							X[8]		X[9]	

3. Safety Lab Sampling for day 1: Pre-study drug, 4 and 12 hours post-study drug

4. Troponin Sampling for day 1: Pre-study drug, and 12 hours post-study drug

5. PK Sampling for day 1: Pre-study drug, 2 minutes post-study drug, 1 and 4 hours post-study drug

6. Biomarker Sampling for day 1: Pre-study drug, 1, 4 and 12 hours post-study drug

7. CMR should be conducted 48-96 hours post-study drug preferably before patient is discharged from hospital.

8. Unblinded analysis of CMRs, 14-day arrhythmias, Troponin levels and ST-segment resolution will be conducted by a separate unblinded team at Covance and rest of Covance study team, Faraday, Investigators, and 3rd party vendors will not be unblinded to individual patient treatments

9. Unblinded analysis of CMRs will be conducted by a separate unblinded team at Covance and rest of Covance study team, Faraday, Investigators, and 3rd party vendors will not be unblinded to individual patient treatments

10. Vital signs (pulse, respiratory rate, blood pressure) will be recorded every 15 minutes after study drug for an hour, then hourly for another 4 hours. There is a +/- 10 minute window on all vital sign collections

11. 12-lead ECG for day 1: at screening for diagnosis of STEMI for inclusion criteria, and to obtain baseline ST-segment elevation, during PCI treatment to document peri-procedural arrhythmias and again at 4 hours post study drug for ST-segment resolution. 3 strips each at screening and 4 hour time point

12. 12-lead ECG including rhythm strip to identify any persistent arrhythmias

13. 12-lead ECG including rhythm strip to identify any persistent arrhythmias

14. Prior to study enrollment written informed consent will be obtained either from the subject or a legally authorized representative of the subject. If study informed consent was given by the subject's legally authorized representative prior to study enrollment, the subject will be provided with a modified consent once they are stable (after investigational drug treatment and STEMI procedure) and in the opinion of the investigator capable of providing written consent. This modified informed consent document will cover the subject's agreement to remain in the clinical trial and proceed with all study related procedures and follow-up.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

The subject or a legally authorized representative must have provided informed consent after the nature of the study has been explained and questions addressed. Subjects must meet the following criteria to be eligible to participate in the study.

6.1 Subject Inclusion Criteria

2. 18-80 year old male subjects
3. 18 to 80 year old female subjects who are not of child-bearing potential.
4. Accepted for Primary PCI with diagnosis of first STEMI, based on clinical and ECG criteria (ST-elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 millivolt (mV) in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads), within 12 hours of symptom onset.

   Written informed consent prior to study participation (either by the subject or a legally authorized representative of the subject)

6.2 Subject Exclusion Criteria

1. Previous myocardial infarction
2. Left bundle branch block (LBBB)
3. Previous coronary artery bypass graft surgery (CABG)
4. Major hemodynamic instability or uncontrolled ventricular arrhythmias.
5. Known contraindication to CMR (e.g. pacemaker)
6. Patients with known thyroid disease, or known allergy to iodide.
7. Subjects with past or current renal impairment requiring dialysis
8. Pregnant or females of child bearing potential
9. Body weight > 120 kg or Body Mass Index (BMI) > 35 kg/m2
10. Use of investigational drugs or devices within 30 days prior to enrollment into the study.
11. Life expectancy of less than 1 year due to non-cardiac pathology
12. Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study

6.3 Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the Institution. Subjects may also be withdrawn from the study at the discretion of the PI.

Any subject who withdraws consent to participate in the study will be removed from the study. Although the subject is not obliged to give his or her reason for withdrawing prematurely from the study, the Investigator should make a reasonable effort to ascertain the reasons while fully respecting the subject's rights.

In the interest of the subject, subjects who withdraw consent or are withdrawn from the study by the Investigator should be encouraged to complete a follow-up visit (early termination visit) as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable CRF.

6.4 Early Termination Visit

At any such early termination visit, the procedures scheduled for the six-month follow-up should be performed.

7 STUDY TREATMENTS

7.1 Description of Study Drug

FDY-5301 is sodium iodide (chemical formula NaI) administered as an isotonic solution for intravenous injection with a concentration of 7.2 mg/mL. The dosage form of FDY-5301 is a small volume parenteral solution. The solution has a pH between 7.0 and 9.5. Normal saline will be used as placebo.

7.2 Concomitant Medications

For all medications taken during the procedure and after, the medication name, total daily dose, route, frequency of dosing and indication for use will be recorded on the concomitant medication page in the CRF.

7.3 Randomization and Blinding

Study treatment will consist of FDY-5301 (3 dose levels) or placebo.

All subjects who fulfill all study eligibility criteria will be randomized to receive one of the 4 treatments allocated by a computer generated randomization code. Clinical staff will be kept unaware of treatment allocation as placebo and active vials will be identical in appearance.

8 STUDY DRUG MATERIALS AND MANAGEMENT

8.1 Study Drug

FDY-5301 will be provided as single use vials for injection containing 20 mL of drug product at a concentration of 7.2 mg/mL. The active ingredient sodium iodide (NaI), and the following inactive excipients: sodium chloride, and water for injection.

Placebo will be provided as single use 20 mL vials for injection containing sterile saline solution.

The manufacturing batch (or box number) of investigational product (active drug, placebo) will be recorded on each subject's drug administration case report form (CSR).

8.2 Study Drug Packaging and Labeling

FDY-5301 final drug product will be manufactured and packaged by Alcami on behalf of Faraday Pharmaceuticals, Inc. in accordance with GMP.

Supply and Return of Drug

Clinical supplies will be shipped to sites following the completion of study initiation and receipt of Institutional Ethics Approval.

Labels will be in accordance with all applicable local regulations and may include:

- For Investigational Use Only
- Site identification
- Subject Number (blank for insertion)
- Batch (Lot) Number
- Storage conditions
- Expiry Date
- Sponsor's Name

8.3 Study Drug Storage

Clinical trial materials will be securely stored as supplied (20 to 25 °C) and should not be stored frozen. Direct exposure to sunlight and heat should be avoided.

The sponsor reserves the right to inspect the drug storage area before and during the trial.

8.4 Study Drug Preparation

The formulation has no preservative and is intended for single use only; injection solutions should be prepared using aseptic technique and inspected prior to administration. The solution for injection should be a clear, colorless solution with no particulate matter.

A guide will provide detailed instructions for randomization and calculation of dose of drug (or volume of placebo) and preparation of the intravenous injection. Drug administration by bolus injection to the subject must occur at any time between 60 minutes and 5 minutes prior to reperfusion of the coronary artery.

8.5 Administration

FDY-5301 will be administered intravenously by a healthcare professional. Dosage will be administered on a body weight basis, according to treatment assignment and using the subject's body weight determined on the dose administration day. Preparation of the administered dose will be achieved by adjusting the volume of undiluted solution of 7.2 mg/mL FDY-5301

8.6 Study Drug Accountability

Study drug will only be used for purposes of this study. The clinical site staff will be responsible for the study drug accountability, reconciliation and record maintenance in accordance with all applicable regulatory requirements. The amount of drug received from Faraday Pharmaceuticals and the amount administered to subjects will be documented.

Investigational Product Accountability

An investigational product accountability record for the investigational products mandated by the protocol must be kept current and should contain:

- The dates and quantities of investigational product received from Faraday Pharmaceuticals, Inc.
- manufacturing batch or box numbers for product received
- subject's identification (subject number and initials)
- date and quantity of investigational product dispensed (and remaining, if from individual subject drug units)
- the initials of the dispenser
- date and quantity of drug returned to the investigator/pharmacy, if appropriate

At the end of the study, the final investigational product reconciliation statement must be completed and provided to Faraday Pharmaceuticals.

These inventories must be made available for inspection by an authorized Faraday Pharmaceuticals representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused trial supplies.

8.7 Study Drug Handling and Disposal

Only subjects randomized into the study may receive study drug. Authorized and adequately trained staff will administer the study drug.

The Principal Investigator must maintain accurate records demonstrating dates and amount of drug received, to whom it was dispensed and accounts of any drug accidentally or deliberately destroyed. It will be the responsibility of the Sponsor to ensure that adequate samples of all trial doses are retained in accordance with the relevant regulatory guidelines.

At the conclusion of the trial, a final inventory will be performed by the Sponsor Monitor and the Principal Investigator or nominees. If any supplies cannot be accounted for, this should be documented on the drug accountability form together with an explanation of the discrepancy. The originals of the drug accountability and dispensing logs must be sent to the Sponsor. The Principal Investigator will retain copies of these logs on file.

Any remaining drug at the end of the study will be disposed of as per sponsor instructions (e.g. at the site by using approved drug destruction methods).

9 REPLACEMENT OF SUBJECTS

Any subject who signs an informed consent form but is not randomized will be considered a screen failure and be replaced. Any subject who receives investigational treatment that does not undergo PCI will be followed up for safety but replaced.

10 CMR PROTOCOL

MRI determination of MSI, MI size, MI/VV, and Cardiac Function

Cardiac MRI (CMR) will be performed at 72 +/- 24 hours and 3 months post-study drug at the study site.

The 72 hour CMR will include cine, T2W and LGE imaging for function, edema and necrosis respectively. The 3 month CMR will include cine and LGE for function and late scar quantification respectively.

The primary estimate of AAR and hence MSI will be based on CMR imaging of myocardium for edema (secondarily the length of coronary artery occluded will be document at the time of PCI).

Cardiac function will be assessed by CMR and defined in terms of EDV, ESV, FS and EF.

All MRI data will be analyzed at a central core laboratory. Detailed instructions for the conduct and interpretation of the CMR will be available in a separate document, including the parameters to be analyzed.

11 STUDY OUTCOMES

Primary Outcome:	The primary outcome for this study will be the combined number and incidence rate of several arrhythmias of interest that occur in each group over a 14 day period post-study drug. These arrhythmias including ventricular fibrillation, sustained ventricular tachycardia (≥125 BPM, ≥ 30 seconds), non-sustained ventricular tachycardia (≥ 125 BPM, ≥ 16 beats, < 30 seconds) and high degree AV block (2^{nd} or 3^{rd} degree, ≥ 8 beats) were chosen because they are significant prognostic indicators of depressed left ventricular ejection fraction and cardiac death [1]. The combined number of arrhythmic events in each group will be calculated along with the arrhythmia incidence rate defined as the percentage of patients in each group experiencing at least one of the defined arrhythmias of interest. An exploratory sub-analysis will be conducted to determine the number and incidence rate of each separate arrhythmia type per dose group. Continuous ECG monitoring will occur from post reperfusion until 14 days post study drug by means of wearable ECG recorders. These will be positioned and activated as soon as feasible after treatment with study drug is complete. Blinded, standardized centralized interpretation will be used for analysis of arrhythmias recorded with the wearable device. Descriptions of peri-procedural arrhythmias such as reperfusion arrhythmias or VF episodes occurring prior to application of the wearable cardiac monitor will be categorized and documented separately on the CRF, with particular emphasis on persistent arrhythmias.
Secondary Outcomes:	• Infarct size parameters will be assessed by CMR at 72 +/- 24 hours and at 3 months; the following will be compared between groups; infarct size as a proportion of ventricular volume (INF/VV), myocardial salvage index (MSI) and absolute MI size • The proportion of patients with ST-segment resolution at 4 hours post study drug • Serum levels of troponin calculated as AUC 0-48 hours post-study drug

	• Serum biomarkers of cardiac injury, inflammation and remodeling out to 3 months of follow up • Persistent arrhythmias at 30 days and 3 months • Measures of cardiac function by CMR including EDV, ESV, FS and EF • Cardiac-related adverse events including the development of heart failure out to three months of follow up. Incidence of all-cause and cardiac mortality out to 6 months of follow up

12 ASSESSMENT OF PHARMACOKINETICS, TROPONIN AND LABORATORY SAFETY MEASURES

12.1 Pharmacokinetics: Blood Iodide Levels

12.1.1 Pharmacokinetic Evaluation

The concentrations of FDY-5301 will be measured in plasma. 6 mL of blood should be collected in a lithium heparin tube. Every effort should be made to collect the PK samples as close to the time points listed below.

- Pre-study drug
- 2 minutes, 1, 4, 24 and 48 hours post-study drug

The pharmacokinetic analysis will include calculations of concentration-time profiles in subjects following dosing with study drug. Mean, standard deviation (SD) and CV will be calculated at each time point. For each dose group, the pharmacokinetic behavior of blood iodide will be described as area under the concentration versus time curve (AUC, AUC_{inf}) the maximal concentration (C_{max}), the time (T_{max}) when the maximal concentration is achieved, the apparent terminal elimination rate (Kel) and terminal half-life ($T_{1/2}$) for each subject. From this information, the total body clearance (CL), and the volume of distribution (V) will be derived.

12.2 General Safety

Safety and tolerability measurements will include:

- Physical examination
- Vital signs, including monitoring of blood pressure, pulse and heart rate
- Blood samples will be collected for hematology, clinical chemistry, coagulation parameters and thyroid function tests
- Adverse events

12.2.1 ECGs

12 lead ECGs will be used to confirm STEMI diagnosis during screening, document peri-procedural arrhythmias during treatment, obtain baseline ST-segment elevation prior to treatment and in order to evaluate ST segment resolution 4 hours post-study drug. In addition, 12 lead ECGs will be used to confirm any persistent arrhythmias at the following time points:

- 30 days post-study drug
- 3 months post-study drug

12.2.2 Biochemistry

Samples will be analyzed for sodium, potassium, chloride, bicarbonate, glucose, urea, urate, creatinine, phosphate, total and, albumin, total protein, total and conjugated bilirubin, GGT, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LD), TSH, T3 and free T4 at the time points listed below:

- Pre-study drug
- 4, 12, 24 and 48 hours post-study drug

12.2.3 Hematology

Samples will be analyzed for ACT (during anticoagulant administration only) hemoglobin, red blood cell count (RBC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, white cell count (WCC), and absolute counts of neutrophils, lymphocytes, monocytes, eosinophils and basophils at the time points listed below:

- Pre-study drug
- 4, 12, 24 and 48 hours post-study drug

12.2.4 Troponin Levels

In order to calculate AUC 0-48 hours, serum troponin T levels will be measured at the following time points:

- Pre-study-drug
- 12, 24, 48 hours post-study drug

12.2.5 Other Biomarkers of Cardiac Injury and Inflammation

Serum biomarkers of cardiac injury, inflammation and remodeling will be measured at the following time points:

- Pre-study drug
- 1,4,12, 24 and 48 hours post-study drug
- 3 months post-study drug

12.3 Laboratory Certification and Reference Ranges

Before the initiation of this trial, the Principal Investigator, or nominee, will provide Faraday Pharmaceuticals, Inc. with a copy of the certification form, with certification number and expiration date for the clinical laboratories used in the trial. Reference ranges for each laboratory test used in this trial will be obtained from the relevant laboratory performing trial tests. In the event the clinical laboratories are changed during the trial, Faraday Pharmaceuticals, Inc. will be

promptly notified of the reason and date of the change and appropriate documentation will be submitted to verify the certification of the new laboratory.

All clinical laboratory tests will be conducted at the investigational site's local laboratory. All accreditation certificates and laboratory reference ranges will be obtained prior to the commencement of the trial at the investigational site.

13 SAFETY: ADVERSE EVENTS

13.1 Definitions

An ***Adverse Event (AE)*** is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered an investigational product (pharmaceutical) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied.

All adverse events occurring after a dose of investigational product observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be reported on the case report form.

Given that this study specifically recruits STEMI patients, the MI itself will not be characterized as an AE.

However, complications arising as a consequence of the MI, for example emergent or worsening heart failure, death, or known arrhythmias will be specifically documented as adverse events in the CRFs.

Adverse events will be followed until resolved or considered stable out to 3 months. The only serious adverse event that will be tracked longer than 3 months is the incidence of death. All-cause mortality and cardiac-related mortality will be documented by phone call to the patient at 6 months. If the patient is unavailable, then mortality status will be obtained through physician/investigator records. The following attributes must be assigned by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, other suspect drugs, and action taken. The investigator may be asked to provide follow-up information.

13.2 Relationship to Study Drug

The principal investigator (PI) will classify every AE according to its relationship to study drug or trial-related procedures. The categories according to World Health Organization guidelines are listed in Table 3.

Table 3: Relationship of AE to Study Drug or Trial-Related Procedures

Rating	Classification	Definition
1	Probable	An AE that: • Occurs at a reasonable time interval after administration of the

		study drug; • Follows a known response pattern to the study drug and; • Cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies
2	Possible	An AE that: • Occurs at a reasonable time interval after administration of the study drug; • Follows a known response pattern to the study drug, but; • Could have been produced by the patient's clinical state or by other therapies
3	Unlikely	• An AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug; • Another etiology is specified

If the AE is classified as unlikely, the PI should provide a likely cause, other illness, concomitant medication, or other.

13.3 Intensity of Adverse Events

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

13.4 Reporting Serious Adverse Events

A serious adverse event is defined as a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to investigational product.

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or results in prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also usually be considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse.

Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms should also be reported.

All SAEs occurring on study must be reported to the medical monitor within 24 hours of occurrence. These include SAEs within 30 days of the last investigational product dose and up to the last formal follow-up observational period, whichever period is longer.

The investigator should notify the Institutional Review Board (IRB) of SAEs occurring at the site in accordance with local procedures, generally within 72 hours after knowledge of the SAE.

The sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of any test drug. Accordingly, prompt notification of any adverse events by investigators to the sponsor is required. The reporting of SAEs will be conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and local regulatory guidelines.

The initial notification will include at least a description of the event, and the subject identification. This information should be supported as needed with written copies of hospital case reports, autopsy reports, and other documents when applicable on the SAE CRF or the site's standard SAE form.

All adverse events reported in this study will be coded using MedDRA. Treatment-emergent adverse events will be listed and summarized per treatment.

14 STATISTICS

14.1 Study Design

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

14.1.1 General Approach/Considerations

Missing observations will be excluded from the analyses; they will not be substituted by estimated values.

Demographics will be tabulated and summarized by descriptive statistics (mean, median, standard deviation, range) for continuous data and frequency tables for discrete data. Physical examination data from baseline and post-study and medical history data at baseline will be listed. All clinical safety and tolerability data will be listed for each subject. Hematology and clinical chemistry will be analyzed by group mean and outlier analyses. Laboratory values outside the laboratory's reference ranges and associated repeat values together with comments as to their clinical significance will be listed separately. Adverse event data will be summarized by group, visit, severity, and relationship to the study drug.

All adverse events reported in this study will be coded using MedDRA 19.1

Standard pharmacokinetic parameters will be calculated for blood iodide levels.

14.1.2 Populations

The safety population includes all subjects who were randomized and received any amount of study drug. Subjects who did not receive any study medication will not be included in the safety population.

The intent-to-treat (ITT) population will include subjects who gave informed consent and were randomized. This is the "full analysis set" of subjects. Subjects are included in the ITT population according to the treatment assigned.

The per protocol population will be a subset of the ITT population and will include subjects who gave informed consent, were randomized, received any amount of study drug, underwent PCI, and underwent an MRI at 72 +/-24 hours and 3 months.

14.1.3 Study Outcomes

The primary outcome for this study will be the combined number and incidence rate of several arrhythmias of interest that occur in each group over a 14 day period post-study drug. These arrhythmias including ventricular fibrillation, sustained ventricular tachycardia (≥125 BPM, ≥ 30 seconds), non-sustained ventricular tachycardia (≥ 125 BPM, ≥ 16 beats, < 30 seconds) and high degree AV block (2^{nd} or 3^{rd} degree, ≥ 8 beats) were chosen because they are significant

prognostic indicators of depressed left ventricular ejection fraction and cardiac death [1]. The combined number of arrhythmic events in each group will be calculated along with the arrhythmia incidence rate defined as the percentage of patients in each group experiencing at least one of the defined arrhythmias of interest.

An exploratory sub-analysis will be conducted to determine the number and incidence rate of each separate arrhythmia type per dose group.

Secondary exploratory efficacy outcomes will include:

Infarct size as a proportion of ventricular volume (INF/VV), the myocardial salvage index (MSI), absolute MI size (INF) at 72 +/- 24 hours and 3 months post study drug measured by CMR.

The proportion of patients with ST-segment resolution at 4 hours post study drug.

Serum levels of troponin calculated as AUC 0-48 hours post study drug.

Cardiac-related adverse events including the development of heart failure.

The incidence of all-cause and cardiac mortality out to 6 months post PCI.

In addition to the measurement of safety and efficacy parameters in this study, serum biomarker levels of cardiac injury, inflammation and remodeling will also be assessed.

14.1.4 Sample Size Estimation

Little data exists on the incidence of arrhythmias that occur over an extended period of time following AMI and monitoring strategies for this type of assessment have not been optimized in a clinical trial setting. The primary goal of our study is to characterize the occurrence of arrhythmias in this patient population for 14 days post-AMI and to determine the feasibility of using ambulatory patch ECG monitors to capture this data. These data should be regarded as exploratory with the objective of identifying a meaningful clinical end point that can be easily measured in future, pivotal studies that are adequately powered to detect differences across treatment groups.

Estimating a drop-out rate of approximately 50%, we will need to enroll up to 160 patients in order to obtain a final total sample size of 80 patients. A final sample size of 80 patients will provide 80% power to detect a 37% reduction in INF/VV assuming an SD of 10%, a 24% increase in MSI assuming an SD of 20% and a 39% reduction in Troponin AUC with an SD of 60%. Equal variance was assumed among groups with an unbalanced allocation of patients to placebo (n=20) and combined FDY-5301 treatment groups (n=60).

14.1.5 Interim and Final Analyses

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

- Safety (14-day arrhythmias)
- 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

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

- Early efficacy outcomes including MSI, INF/VV, INF
- Cardiac function including EDV, ESV, FS and EF

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

14.1.6 General Analysis of Safety and Efficacy Outcomes

Analysis of the primary safety outcome: characterize the number and incidence rate of serious arrhythmias that occur during a 14-day interval in this patient population. No hypothesis will be tested and data will be descriptive in nature only. A more detailed analysis strategy will be outlined in the SAP.

Analysis of exploratory secondary efficacy outcomes: For all variables with a continuous outcome including infarct size relative to the VV, MSI, absolute MI size, cardiac function, biomarkers of cardiac injury and cardiac troponin levels, a single pairwise comparison to analyze differences between all three FDY-5301 groups (combined) and placebo will be used. 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. Each group will then 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.

For categorical outcome including ST-segment resolution and incidence of all-cause and cardiac related mortality or morbidity, odds ratios comparing each FDY-5301 treatment group with placebo will be calculated.

Physical examination data from baseline, post-study and **medical history** data at baseline and peri-procedural arrhythmia data will be listed by patient. All clinical safety and tolerability data will be listed for each subject. **Laboratory values** will be calculated as group mean data and presented in shift tables. Comments as to the clinical significance of out of range values will be listed separately. **Adverse event** data will be summarized by group, visit, severity, and possible relationship to the study drug.

14.1.7 Pharmacokinetic Data Analysis

The concentration of iodide in blood (at different time points and doses) will be summarized for each group. The pharmacokinetic analysis will include collections of a concentration-time profile in subjects following dosing with study drug. Mean, standard deviation (SD) and CV will be calculated at each time point. The pharmacokinetic behavior of blood iodide will be described as

area under the concentration versus time curve (AUC, AUC_{inf}) the maximal concentration (C_{max}), the time when the maximal concentration is achieved (T_{max}), the apparent terminal elimination rate (Kel) and terminal half-life ($T_{1/2}$) for each subject. From this information, the total body clearance (CL), and the volume of distribution (V) will be derived.

15 ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki and the ICH guidelines for GCP. Faraday will ensure that the study complies with all local, federal or country-specific regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject identification number that should be used on all forms associated with the subject's samples or documents that will be supplied to the Sponsor (or CRO) or to any party completing testing on behalf of the Sponsor (e.g., samples for central laboratory analyses). Data privacy will be maintained according to local and federal requirements and will not be released without the written permission of the subject (or the subject's guardian), except as necessary for monitoring and auditing by Faraday, its designee, the FDA or other applicable regulatory authority, or the IRB/IEC.

All unpublished information concerning the study drug, as well as any information concerning the business or operations of Faraday Pharmaceuticals or its affiliates that have been provided by or on behalf of the Sponsor to the Principal Investigator and all employees and coworkers involved with this study ("Study Personnel"), are confidential and will remain confidential information and sole property of Faraday. This includes, without limitation, information concerning the clinical indications for the study drug, its formula, methods of manufacture, regulatory, marketing and strategic information, and all other scientific, nonclinical or clinical data relating to it. Study Personnel must agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission is obtained from Sponsor's authorized representative, and not to disclose, or use Sponsor's confidential information for any purpose other than performance of the study. Prior written agreement from the Sponsor's authorized representative must be obtained for the disclosure of any said confidential information to other parties.

15.2 Study Monitoring

Covance is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the CRFs. Subject confidentiality will be maintained during this process.

In accordance with applicable regulations, GCP and Covance standard operating procedures, the study monitor will visit the site prior to subject enrollment to review the protocol and data collection procedures with site staff. The study monitor will also conduct periodic on-site visits.

During these on-site visits, the monitor will:

- Review study progress

- Review study data collected
- Conduct source documentation verification

Data recorded on subject's CRF will be source document verified by the study monitor. CRFs will be forward to the contracted Data Management group and data entered, verified and corrected according to the Statistical Analysis Plan.

The subjects' CRFs and supporting documents will be reviewed and confidentiality will be maintained at all times. Direct access source data verification (SDV) will occur in this trial. Parameters checked for 100% of subjects entered into the trial will include, but not be limited to, the following:

- Subject ID number and initials
- Date of birth
- Presence of signed informed consent
- Gender
- Eligibility criteria
- Concomitant medication
- Visit dates
- Adverse events
- Compliance with drug administration
- Key safety variables

The investigator agrees to allow the study monitor direct access to all relevant study-related documents and to set aside time to discuss any relevant findings or issues.

Study closure will involve the following activities with site staff and investigator(s):

- Return of all study-related material to the sponsor
- Resolution of outstanding data queries
- Accountability, reconciliation and arrangements for unused investigational product
- Review of site study records for completeness

15.3 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of human subjects in research studies. Prior to the study onset, the protocol, informed consent, advertisements or materials to be used for subject recruitment, and any other written information to be provided to the subject must be approved by the IRB/IEC. Any amendments to the protocol or informed consent will require review and approval by the IRB/IEC before the changes are implemented to the study. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH Guideline E6 will be maintained by the site and will be available for review by Faraday or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number, and the date that approval and/or a favorable opinion was granted.

The Principal Investigator or authorized designee is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or as otherwise specified by the IRB/IEC. The Principal Investigator or Sub-Investigator must supply Faraday or its designee with written documentation of continued review of the clinical research.

The IRB/IEC is expected to maintain the confidentiality of the protocol and related information.

16 QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial-related site source data, study-related documents and reports will be available, and that the provision of direct access for monitoring and auditing by Faraday or its designees will be permitted. In addition, the Investigator must ensure that all trial-related site source data, study-related documents, and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/EC/IEC.

The Investigator is responsible for notifying Faraday in advance of an impending regulatory inspection. He/she may request that Faraday provide support for preparation, if necessary, and is required to provide updates on the ongoing activities during the inspection and submit any citations/objectionable findings (i.e., FDA 483) and is required to share any follow up responses to the outcome.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Study Monitor (source document verification). The Monitor will also review the Investigator's drug accountability records to ensure that the drug supplies are stored and dispensed appropriately. A comprehensive validation program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Faraday or its designates may review data as deemed necessary.

17 INFORMED CONSENT

A written informed consent in compliance with Part 50 of Title 21 of the Code of Federal Regulations (CFR), with the Declaration of Helsinki, ICH guidelines, federal and/or local regulations, and advance approval by the Institutional Review Board (IRB)/Ethics Committee (EC)/Independent Ethics Committee (IEC) shall be obtained from each subject or a legally authorized representative of the subject prior to entering the study or performing any unusual or non-routine procedure that involves risk to the subject, including washout of any medications. The decision of whether to obtain written consent directly from the subject will be determined by the investigator. If, in the opinion of the investigator, the subject is not in a state to fully provide written consent, the investigator will obtain written consent from a legally authorized representative of the subject.

Before enrollment, each prospective subject or legally authorized representative of the subject will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the Principal Investigator or authorized designee is assured that the subject or legally authorized representative of the subject understands the implications of participating in the study, the subject or legally authorized representative of the subject will be asked to give consent to participate in the study by signing the informed consent form.

If study informed consent was given by the subject's legally authorized representative prior to study enrollment, the subject will be provided with a modified consent once they are stable (after investigational drug treatment and STEMI procedure) and in the opinion of the investigator capable of providing written consent. This modified informed consent document will cover the subject's agreement to remain in the clinical trial and proceed with all study related procedures and follow-up.

The consent forms must be dated and retained by the Investigator as part of the clinical trial records. The Investigator will not undertake any investigation specifically required for the clinical trial until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF. Each subject will receive a fully-signed copy of each consent form that he/she signs for the clinical trial

The Principal Investigator is responsible for maintaining the originally signed ICF document according to record retention requirements.

If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor and/or its designee, if appropriate, prior to IRB/IEC submission. Once reviewed, the consent will be submitted by the Principal Investigator or authorized designee to his or her IRB/IEC for review and approval prior to the start of the study. If the informed consent form is revised during the course of the study, all actively

participating subjects must sign the revised form, unless otherwise indicated, i.e. administrative changes.

If subject or subject's partner, becomes pregnant during their participation in the trial, a separate pregnancy informed consent form will be obtained, to follow the pregnancy, any complications, and the health of the baby. The pregnancy consent should be obtained at the time the investigator becomes aware of the pregnancy.

18 PROTOCOL DEVIATIONS

The Principal Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC and agreed to by the Principal Investigator. Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal Investigator will be notified of violations and/or deviations in writing by the monitor. The IRB/IEC should be notified of all protocol violations and deviations according to IRB/IEC reporting requirements.

19 DATA HANDLING AND RECORDKEEPING

19.1 Reporting and Recording of Data

It is the responsibility of the Investigator to record essential information in the medical records in accordance with local regulations and requirements. The Investigator is responsible for ensuring the accuracy, completeness, legibility and timelines of the data recorded in the eCRF.

The Principal Investigator agrees to maintain accurate source documentation as part of the case histories and to accurately enter this information on to the electronic Case Report Forms (eCRFs). These source documents are distinct from the eCRFs and are designed to record all observations and other data pertinent to the investigation on each subject.

The eCRFs will be reviewed and the source documents verified by the study monitor during routine monitoring visits, in accordance with the Clinical Monitoring Plan, to ensure that data in the eCRFs are accurate and complete.

19.2 Retention of Records

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Faraday.

Faraday will notify the Investigator/institution when the study records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records must be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to Faraday.

The Investigator must inform Faraday immediately if any documents are lost, to be transferred to another facility, or to be transferred to a different owner.

The Investigator must contact Faraday prior to destroying any records associated with the study.

19.3 Confidentiality and Publications

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on CRFs and other documents by their subject number, initials and/or birth date, not by name and subject in accordance with local requirements. Documents not to be submitted that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

Faraday is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles. Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Faraday before submission for publication. Names of all Investigators participating in the study will be included in the publication. The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria for authorship. That is, all authors must meet each of the following 3 criteria:

- Substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data
- Drafted the article or revised it critically for important intellectual content
- Approved the final version for publication

Members of the study steering committee generally fulfill the authorship criteria through their involvement in protocol design and review, monitoring of and sometimes direct involvement with recruitment, and thus they will usually be part of the publication committee. If studies are multicenter, it may be appropriate to assign group authorship.

In addition, certain Faraday employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician and study project manager or their equivalents.

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20 REFERENCES

1. Poul Erik Bloch Thomsen, MD; Christian Jons, MD; M.J. Pekka Raatikainen, MD; Rikke Moerch Joergensen, MD; Juha Hartikainen, MD; Vesa Virtanen, MD; J. Boland, MD; Olli Anttonen, MD; Uffe Jakob Gang, MD; Nis Hoest, MD; Lucas V.A. Boersma, MD; Eivin S. Platou, MD; Daniel Becker, MSc; Marc D. Messier, PhD; Heikki V. Huikuri, MD; (2010). Long-Term Recording of Cardiac Arrhythmias With an Implantable Cardiac Monitor in Patients With Reduced Ejection Fraction After Acute Myocardial Infarction The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study. *Circulation*. 121:1258-1264. DOI: 10.1161/CIRCULATIONAHA.109.902148