Supplementary Material

A Randomized, Double-Blind, Dose Ranging Clinical Trial of Intravenous FDY-5301 in Acute STEMI Patients Undergoing Primary PCI

David Adlam Dhil FRCP [1], Maciej Zarebinski MD [2], Neal G. Uren MD FRCP [3], Pawel Ptaszynski MD, PhD [4], Keith G. Oldroyd MD FRCP [5], Shahzad Munir MD [6], Azfar Zaman MD [7], Hussain Contractor MBChB DPhil [8], Róbert Gábor Kiss [9], István Édes [10], Joanna Szachniewicz [11], Gergely Gyorgy Nagy MD PhD [12], Mario J. Garcia MD, FACC[13], János Tomcsanyi MD, PhD [14], John Irving MD [15], Andrew S.P. Sharp MD [16], Piotr Musialek MD DPhil [17], Géza Lupkovics [18], Cheerag Shirodaria MD[19], Joseph B. Selvanayagam MBBS (Hons) FRACP DPhil [20], Pauline Quinn [1], Leong Ng [1], Mark Roth PhD [21], Michael A. Insko [21], Ben Haber [21], Stephen Hill [21], Lori Siegel [21], Simon Tulloch [21], Keith M. Channon MD FRCP [22]

1. Department of Cardiovascular Sciences, NIHR Leicester Biomedical Research Centre, University of Leicester, UK
2. Invasive Cardiology Dept. Western Hospital, Grodzisk Mazowiecki, Poland
3. Edinburgh Heart Centre, Royal Infirmary, Edinburgh, UK
4. Department of Electrocardiology, Medical University of Lodz, Poland, Central University Hospital, Lodz, Poland
5. West of Scotland Regional Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, UK
6. Cardiology Department, Wolverhampton Heart and Lung Centre, New Cross Hospital, Wolverhampton Road, Wolverhampton, UK
7. Freeman Hospital and Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK
8. Department of Cardiovascular Medicine, Manchester University NHS Foundation Trust, Wythenshawe Hospital, Manchester, UK
9. Department of Cardiology, Military Hospital, Budapest, Hungary
10. Department of Cardiology, Debrecen University, Debrecen, Hungary
11. Centre for Heart Diseases, Military Hospital, Wroclaw, Poland
12. Borsod-Abauj-Zemplen County Central Hospital and University Teaching Hospital, 1st Department of Internal Medicine and Cardiology, Miskolc, Hungary
13. Division of Cardiology, Montefiore Medical Center, Bronx, New York
14. Department of Cardiology, St. John of Brother of God Hospital, Budapest, Hungary
15. Department of Cardiology, Ninewells Hospital, Dundee, United Kingdom
16. Consultant Cardiologist, University Hospital of Wales, Cardiff. Honorary Associate Professor, University of Exeter.
17. Jagiellonian University Department of Cardiac and Vascular Diseases, John Paul II Hospital, Krakow, Poland
18. Department of Cardiology, St. Raphael Hospital of Zala County, Zalaegerszeg
19. Covance Clinical and Periapproval Services Limited, Maidenhead, UK
20. Flinders University and South Australian Health and Medical Research Institute, Adelaide, SA, Australia
21. Faraday Pharmaceuticals Inc., Seattle, USA
22. Division of Cardiovascular Medicine, British Heart Foundation Centre of Research Excellence, National Institute for Health (NIHR) Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and University of Oxford, John Radcliffe Hospital, Oxford, UK

Supplementary Materials and Methods

Supplementary Materials and Methods

Study Conduct

This was a Phase 2, randomized, double-blind, placebo-controlled, multi-center study that evaluated the safety, pharmacokinetics and preliminary efficacy of FDY-5301 in patients with acute STEMI undergoing PPCI. The study design and conduct were overseen by a Study Management Group consisting of investigators, representatives of Faraday Inc. and a contract research organization (Covance Inc.). An independent Data and Safety Monitor had full access to unblinded data. Final statistical analysis was conducted by Covance in collaboration with the investigators and sponsor. The trial was conducted in accordance with GCP and the declaration of Helsinki and was approved by appropriate Ethics committees under an IND (USA) and CTA (Europe), with CT.gov and EudraCT numbers NCT03470441 and 2017-000047-41, respectively.

Study Patients

Patients were eligible for enrollment if presenting with a first-time STEMI as evidenced by typical chest pain and diagnostic ECG features, with a view to PPCI within 12 hours of pain-onset. The ECG criteria were 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. Major exclusion criteria were previous myocardial infarction; left bundle branch block (LBBB); previous coronary artery bypass graft surgery (CABG); major hemodynamic instability or uncontrolled ventricular arrhythmias; known contraindication to CMR (e.g. pacemaker); patients with known thyroid disease or known allergy to iodide; subjects with past or current renal impairment requiring dialysis; body weight >120 kg or body mass index (BMI) >35 kg/m^2.

Patients gave either verbal assent in the emergency setting,[1] followed by informed consent after the emergency procedure, or informed consent at the time of recruitment consistent with local and national regulations.

Study Treatment

Patients were randomized by an online algorithm to receive a single dose of either placebo, 0.5 mg/kg FDY-5301, 1.0 mg/kg FDY-5301 or 2.0 mg/kg FDY-5301, prior to PPCI. The doses of FDY-5301 spanned the effective dose range effective for myocardial protection reported from preclinical studies[5,6] and were <20% of the maximal safe dose tested in the phase 1 study ACTRN12616001165471, (Supplementary figure 1). The blinded study medication was drawn up from coded vials based on estimated body weight and administered as a single intravenous bolus via a peripheral cannula, between 60 and 5 minutes prior to opening of the culprit lesion. Timing of administration of study medication with respect to coronary arterial reperfusion was recorded.

Coronary Angiography and PCI

Excepting the administration of study treatment, patients were otherwise managed at the discretion of their clinical team and in accordance with local treatment guidelines for the management of STEMI. Patients received antiplatelet therapy and intravenous anticoagulation, according to usual clinical practice. Coronary intervention was performed using a guiding catheter via the radial or femoral artery. Epicardial coronary reperfusion was established by passage of a coronary guidewire, followed

by use of thrombus aspiration catheter and/or balloon pre-dilatation. The culprit lesion was treated with intracoronary stent deployment and dual antiplatelet therapy with aspirin and clopidogrel, prasugrel or ticagrelor for 12 months. Other medications were prescribed according to standard clinical practice.

Arrhythmia Monitoring

Periprocedural arrhythmias were documented by investigators. After the procedure, an adhesive continuous remote ECG monitoring sensor (SEEQ™ Mobile Cardiac Telemetry System; Medtronic, Boston, MA) was applied to patients' chests and replaced as needed for up to 14-days following administration of study drug. The data were analyzed blinded to treatment allocation for the incidence and frequency of pre-determined arrhythmias of interest. These were defined as: ventricular fibrillation; sustained ventricular tachycardia (≥125 bpm, ≥30 seconds); non-sustained ventricular tachycardia (≥125 bpm, ≥ 16 beats, 0<30 seconds), high degree AV block (2^{nd} or 3^{rd} degree, ≥8 beats) and new-onset atrial fibrillation.

CMR Acquisition and Analysis Methods

CMR was performed at 72 hours and three months post-treatment using either a 1.5 or 3.0 T platform. Cine imaging with steady-state free precession (SSFP) and Late Gadolinium Enhancement (LGE) imaging were performed in long-axis views and consecutive short-axis slices covering the entire left ventricle from base to apex. Typical parameters for SSFP imaging were repetition time of 3.0 ms, echo time of 1.5 ms; flip angle of 60°; temporal resolution of 35 ms, in plane resolution of 1.4-1.7 mm, slice thickness of 7 mm, and 3-mm gap. The LGE CMR was performed using a segmented inversion-recovery sequence (in-plane spatial resolution 1.7-1.4 mm; temporal resolution 160 to 200 ms) 10 min after contrast administration (gadoterate meglumine [Dotarem], Guerbet inc; 0.1 mmol/kg). Inversion times were adjusted in the standard fashion to null viable myocardium, typically 280 to 360 ms. To evaluate myocardial edema, a breath-hold, black blood, short-T1 triple inversion recovery pulse sequence was applied with the following parameters; repetition time (TR), 2 x R-to-R intervals, echo time (TE) of 65ms (Philips scanners: 100 ms) and inversion time (TI), 140ms, field of view 34 to 38 cm, matrix 256x256 (or 256 x 192). Short axis T2 images were acquired using the same slice thickness/gap as the cines and late enhancement images. Quantitative and qualitative analysis was performed offline blinded to patient details using Circle CVi42 software (v. 5.9.3, Circle Cardiovascular Imaging, Calgary, Canada) by an independent central core lab (Cardiac Imaging Research, South Australia Health Medical Research Institute, Adelaide, Australia). LV volumes and function were calculated. Infarct size was quantified semi-automatically on LGE imaging using the 5 standard deviation method (5SD technique) and expressed as %LV volume.

Outcome Measures

The predefined primary safety outcome required by one of the national drug regulatory authorities was the combined number and incidence rate of the predefined arrhythmias with an exploratory subgroup analysis for each separate arrhythmia. These were: Ventricular fibrillation, persistent supraventricular tachycardia, persistent premature ventricular contractions, prolonged ventricular tachycardia, multifocal ventricular arrhythmias, atrioventricular heart block, or persistent atrial fibrillation.

The following were predefined secondary outcome measures:

1. Infarct size parameters assessed by CMR at 72 hours and 3 months post-treatment, expressed as Infarct size as % LV volume, and Myocardial Salvage Index defined as (1-final infarct size/area at risk X 100%). Area at risk was measured at the early (3 day) CMR.
2. Measures of cardiac function by CMR including end-diastolic volume index (EDVi), end-systolic volume index (ESVi) and left ventricular ejection fraction (LVEF) at 72 hours and three months post-treatment.
3. The proportion of patients with ST-segment resolution at 4 hours post study drug.
4. Serum troponin concentrations calculated as AUC 0-48 hours post-treatment.
5. Persistent arrhythmias at 30 days and 3 months.
6. Cardiac-related adverse events including the development of heart failure out to three months of follow up.
7. Incidence of all-cause and cardiac mortality out to 6 months of follow up.
8. Serum biomarkers of cardiac injury, inflammation and remodeling out to three months of follow up.

Biochemistry and Hematology Assessments

Blood samples were collected from each patient prior to treatment and at 4, 12, 24 and 48 hours post-treatment, and were analyzed for thyroid function (TSH, T3 and T4), 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), and lactate dehydrogenase (LD). Hematology assessments included hemoglobin and complete blood cell count.

Serum biomarkers for cardiac injury, inflammation and remodeling, [2-14] were analyzed at baseline (0 hour) prior to treatment and at two time-points post-treatment. $AUC_{0\text{-}48}$ for troponin was calculated using the linear trapezoidal method. Myeloperoxidase (MPO) was analyzed at 0, 4, and 24 hours. Pro-brain natriuretic peptide (NT-proBNP), and matrix metalloproteinase-2 (MMP-2) were analyzed at 0, 24 and 48 hours.

Quantification of Plasma Iodide

Faraday has developed a new method to quantify plasma iodide levels ranging from very low (ng/mL) to >1000 fold higher. Plasma sodium iodide concentrations were measured using ion chromatography with amperometric detection. Details are provided in the Supplementary Materials and Methods section.

Definition of Adverse Events

An ***Adverse Event (AE)*** was 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 could 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 was 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), were reported on the case report form. Given that this study specifically recruits STEMI patients, the MI

itself was 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 were specifically documented as adverse events in the CRFs. Adverse events were followed until resolved or considered stable to 3 months. The only serious adverse event tracked longer than 3 months was the incidence of death. All-cause mortality and cardiac-related mortality was documented by phone call to the patient at 6 months. If the patient was unavailable, then mortality status was obtained through physician/investigator records. The following attributes were assigned by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, other suspect drugs, and action taken. Relatedness to the investigational product was categorised into 'unlikely', 'possible' or 'probable' and severity as 'mild', 'moderate' or 'severe' in accordance with standard World Health Organisation guidelines.

A ***Serious Adverse Event*** was 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 was any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening (NOTE: The term "life-threatening" in the definition of "serious" referred to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it did not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- Required inpatient hospitalization or results in prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Was a medically important event or reaction

Medical and scientific judgment were exercised in deciding whether reporting was 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 were also usually be considered serious. Examples specified in the protocol 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 were also specified for reporting. All SAEs occurring on study were reported to the medical monitor within 24 hours of occurrence. These included SAEs within 30 days of the last investigational product dose and up to the last formal follow-up observational period, whichever period was longer. The investigator notified 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 reporting of SAEs was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and local regulatory guidelines.
The initial notification included at least a description of the event, and the subject identification. This information was 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 were coded using MedDRA. Treatment-emergent adverse events were listed and summarized per treatment.

Plasma biomarker assays

Plasma NT-proBNP assay was measured using an in-house non-competitive immunoluminometric assay as previously described.[15] Standards and samples were incubated in ELISA plates coated with a mouse monoclonal IgG directed to the C-terminal of NT-proBNP (100 ng/well). After incubation, plates were developed using a biotinylated sheep N-terminal antibody followed by MAE (methyl-acridinium ester)-labelled streptavidin on a Promega Glomax Multidetection system (Promega UK Ltd, Southampton, UK), using sequential injections of hydrogen peroxide in nitric acid and cetyl trimethylammonium bromide in sodium hydroxide and measuring the relative light unit outputs. This highly specific assay shows no cross-reactivity with ANP (atrial natriuretic peptide), BNP or CNP (C-type natriuretic peptide).

Plasma MMP-2 and MPO were assayed using antibodies obtained from R&D systems Inc. (Minneapolis, USA). Capture antibodies were diluted in phosphate-buffered saline and coated onto ELISA plates. After washing, plates were blocked using bovine serum albumin. Samples and standards were incubated on the plates for two hours, and after washing, the biotinylated detection antibody was incubated within the ELISA plate wells for another two hours. Finally, plates were developed using the MAE (methyl-acridinium ester)-labelled streptavidin and read on a Promega Glomax Multidetection system as described above. The assay antibodies were highly specific for MMP-2 and MPO, with no cross reactivity with other MMPs.

Quantification of plasma iodide

Plasma aliquots were processed in AQ Brand 2mL glass vials (#9509C-WCV-AQ) and Basik caps (#9502C-40T-S) and eluted with A Supp 5 eluent 1.2x w/ 5% Acetonitrile (#ERA-IC1100) 3.8mM Sodium Carbonate/ 1.2mM Sodium Bicarbonate/ 5% Acetonitrile. Sodium iodide concentrations were measured using Metrohm 850 Professional Ion Chromatography (IC) AnCat – MSM High Capacity - MCS (2.850.3040) with 889 IC Sample Center (2.889.0010) with 100uL injection volume instrument and Metrosep A Supp 5 – 150/4.0 (Metrohm #61006520) with Metrosep A Supp 4/5 Guard/4.0 (#61006500) columns. Amperometric detection methods were utilized with DC mode 0.1V Potential: 850 IC Amperometric Detector Compact (#28509110), Ag Working Electrode 3mm (#61257240), Ag/AgCl/KCl Reference Electrode (#61257720), wall jet cell (#65337000) and analyzed using MagIC Net 3.1 software.

Plasma sodium iodide pharmacokinetic characterization

The following PK parameters were 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

As the intravenous bolus model was used, C_0 (back-extrapolated concentration at time zero) was calculated by excluding the observed pre-dose concentration value and then using a log-linear regression of the first 2 post-dose data points to back-extrapolate to the concentration at time 0.

Statistical Analyses

Arrhythmia Incidence Rates

The primary outcome for this study was the combined number and incidence rate of several arrhythmias of interest for 14 days post-study drug. The combined number of arrhythmic events as well as the number of patients in each treatment group experiencing those arrhythmic events was calculated along with the arrhythmia incidence rate defined as the number of patients in each treatment group experiencing an arrhythmia of interest events divided by the total person-time within each treatment group (or the overall FDY-5301 group), expressed as a percentage. Arrhythmia rates were analyzed in first 48 hours since the PPCI, reflecting the known higher incidence of arrhythmias early after acute STEMI, and from 2 to 14 days after PPCI.

Infarct Size Parameters by CMR

Infarct size and cardiac function were assessed by CMR at 72±24 hours post-study drug and three months post-study drug.

A single pairwise comparison was performed for comparison of all three FDY5301 groups (overall) vs. placebo at both the 72-hour and 3-month post-study drug timepoints. An unpaired Student's t-test

was used for the pairwise comparison if the data was normally distributed and a Mann-Whitney rank test was used for non-parametric data. Normality was 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 were produced. Separate comparisons of each treatment vs. placebo were also conducted using a one-way analysis of variance (ANOVA) followed by a Dunnett's post-test or by using a Krustal-Wallis analysis followed by Dunn's post-test for non-parametric data.

The same summarization method and statistical analyses was repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct location (anterior or other). Additionally, the number of patients with a final infarct size of >19% of LV (as previously validated [16]) were analyzed by treatment group. Odds ratios were 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 were repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct location (anterior or other).

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

The number of patients with ST-segment resolution were tabulated by treatment group. Odds ratios were 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 were repeated by baseline TIMI flow (grade 1 and lower, or, grade 2 and 3) and infarct type (anterior or other).

Serum Troponin Concentrations

The troponin $AUC_{4\text{-}48}$ were derived from the serum levels of troponin collected at the following timepoints: pre-dose, 4, 12, 24 and 48 hours post-study drug. $AUC4_{4\text{-}48}$ was calculated using the linear trapezoidal method and adjusted to account for pre-dose serum troponin concentrations. Where possible, the derivation was carried out using actual post-dose times recorded. If actual times were missing, nominal times were used.

Summary statistics (also including geometric means and geometric coefficient of variation [CV] %) for the serum levels were produced by each treatment group for the derived $AUC_{4\text{-}48}$. The summary statistics for troponin $AUC_{4\text{-}48}$ were presented in a similar way. The derived $AUC_{4\text{-}48}$ was logarithmically transformed, and an unpaired Student's T-test was used analyze its differences between all three FDY-5301 groups (overall) and placebo.

Separate comparisons of the logarithmically transformed $AUC_{4\text{-}48}$ from each treatment vs. placebo were also conducted using a one-way analysis of variance (ANOVA) followed by a Dunnett's post-test. The arithmetic least squares means of the treatment differences were back-transformed to provide the geometric means and its 95% confidence interval.

Plasma Biomarker Analysis

Data analysis for the biomarkers (MPO, MMP-2, and NT-proBNP) was performed using GraphPad Prism version 8.2.1. Paired t-test comparisons were performed to evaluate differences in plasma biomarker concentrations over time between all three FDY-5301 groups (combined) and placebo.

Programming Specifications

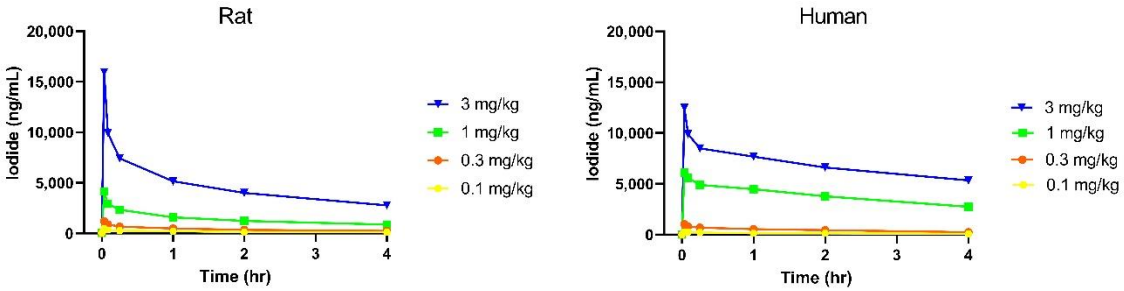
Data analysis was performed using SAS® Version 9.4 or higher, Stata Version 14, GraphPad Prism version 8.2.1, Phoenix WinNonlin (Version 6.4 or higher).

Analysis Data Model (ADaM) datasets were 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 were utilized to ensure compliance with CDISC standards.

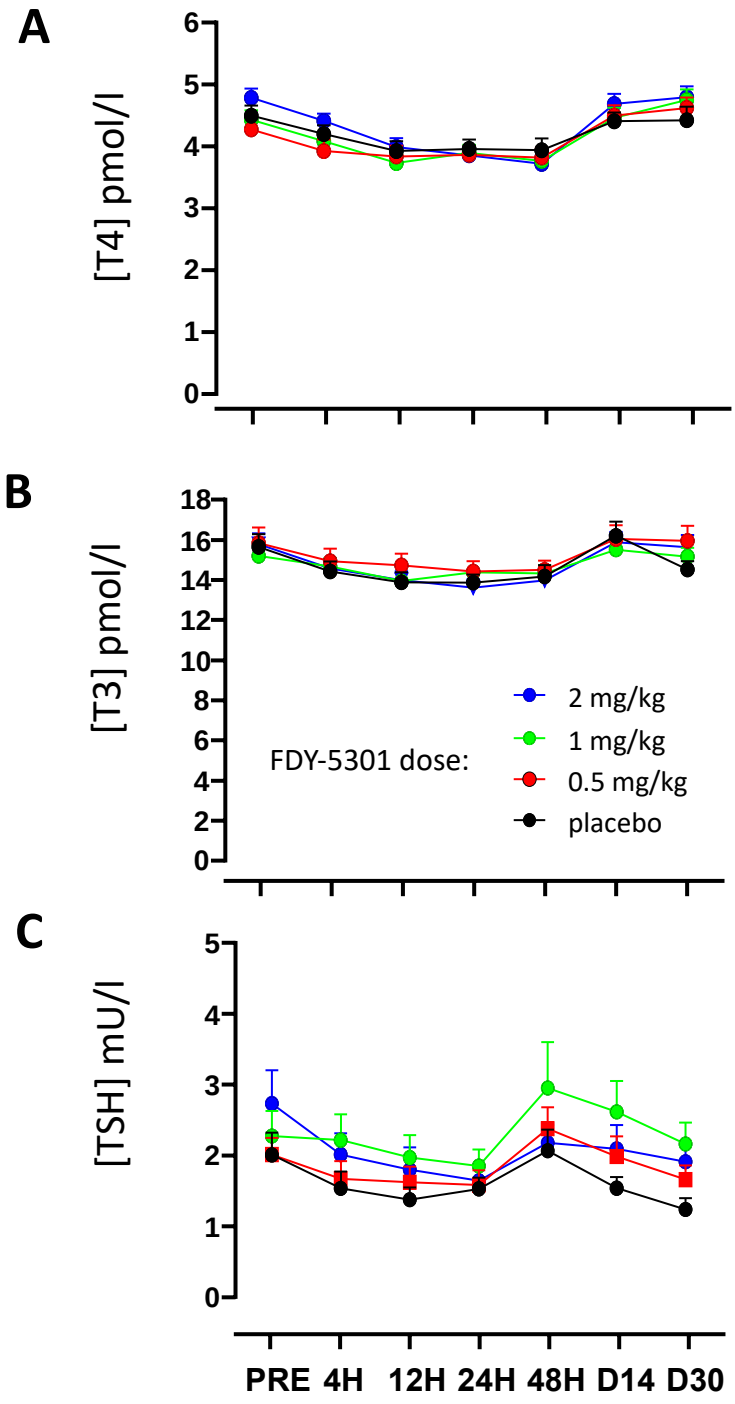
Exploring the impact of potential confounding variables

As part of an exploratory analysis any imbalances between the treatment groups in characteristics that have demonstrated an impact on infarct size and ejection fraction in preclinical and/or clinical studies were investigated. Using the approach of Festic *et al*. [17] following univariate analysis existing knowledge and the evidence in literature was used to group the variables into two sub-groups: one containing variables with beneficial (protective) effects on infarct size and ejection fraction and another sub-group of variables with harmful effects on these outcomes. A random effects model and odds ratio (OR) estimate with 95% confidence interval was then used to determine the pooled probability of a beneficial or harmful effect on outcome.

Supplementary Figures and Tables



Supplementary Figure 1: FDY-5301, a formulation of sodium iodide as an isotonic solution (pH 7.4-8.4), was administered as an IV bolus or infusion over a dose range of 0.1, 0.3, 1, and 3mg/kg in rat preclinical studies and at the same doses plus 10 mg/kg (data not shown) in 40 healthy volunteers in a Phase I, ascending dose, randomized, blinded, placebo-controlled, single-center study and appeared safe and well-tolerated in these subjects (ACTRN12616001165471).



Supplementary Figure 2 – Thyroid Function After Administration of FDY-5301

The levels of thyroxine (T4, Panel A), tri-iodothyroxine (T3, Panel B) and Thyroid Stimulating Hormone (TSH, Panel C) were assayed in plasma at baseline and at 4, 12, 24, and 48 hours and at 14 and 30 days after administration of either placebo or FDY-5301. Points show mean ± SEM.

SUPPLEMENTARY TABLE 1. SUMMARY OF PATIENT DISPOSITION

n	**Placebo**	**0.5 mg/kg FDY-5301**	**1.0 mg/kg FDY-5301**	**2.0 mg/kg FDY-5301**
Randomized	29	29	31	31
14-Day Arrhythmia Monitoring	26	28	29	29
3-Month Infarct Size by CMR	15	24	14	22
3-Month Infarct Size by CMR in Patients with TIMI 0-1	14	17	11	21

SUPPLEMENTARY TABLE 2. DISTRIBUTION OF PATIENTS WHO DID NOT HAVE FOLLOW-UP CMR

	Placebo	**0.5 mg/kg FDY-5301 n**	**1.0 mg/kg FDY-5301 n**	**2.0 mg/kg FDY-5301 n**
Metal/Pacemaker/Other Contraindication	1 (1)	-	2 (2)	-
Poor Quality Scan/Technical Issues	2 (4)	2 (2)	4 (6)	2 (3)
Takotsubo Cardiomyopathy or Other Non-MI	3 (3)	-	1 (1)	1 (1)
Withdrawal of Consent Due to Claustrophobia or Other	6 (6)	3 (3)	7 (7)	3 (3)
Deceased or Medically Unable	-	-	1 (1)	2 (2)

Values without parentheses in each column represent the number of patients in each treatment group with missing 3-month cardiac function data.

Values within parentheses in each column represent the number of patients in each treatment group with missing 3-month infarct size data.

SUPPLEMENTARY TABLE 3. PHARMACOKINETIC ANALYSIS OF FDY-5301 IN STEMI PATIENTS

	AUC_{last} (h*ng/mL)	C_0 (ng/mL)	C_{max} (ng/mL)	$T_{1/2}$ (h)	CL (mL/min)
0.5mg/kg FDY-5301					
Mean	44700	4740	4590	16.3	17.4
SD	21300	1060	1030	4.35	7.16
Median	36700	4900	4760	15.5	16.2
Min	19400	2340	2234	8.73	7.33
Max	94800	7090	6902	24.9	30.9
n	22	24	24	21	20
1mg/kg FDY-5301					
Mean	87200	8580	8290	16.7	16.5
SD	34500	2010	1970	3.49	5.93
Median	88700	8710	8500	16.7	18.2
Min	42700	4130	4084	11.1	9.19
Max	155000	12200	11855	22.2	25.2
n	21	24	24	19	19
2mg/kg FDY-5301					
Mean	130000	17800	17000	13.0	23.3
SD	60400	4920	4330	3.33	7.63
Median	113000	17400	16800	11.7	24.2

Min	57300	8750	8444	9.69	9.05
Max	328000	28000	26757	21.3	36.6
n	24	25	28	22	22

SUPPLEMENTARY TABLE 4. ARRHYTHMIAS OCCURRING DURING THE FIRST 48 HOURS POST-TREATMENT

	Placebo (n=26)	0.5 mg/kg FDY-5301 (n=28)	1.0 mg/kg FDY-5301 (n=29)	2.0 mg/kg FDY-5301 (n=29)	All FDY-5301 (n=86)	Overall (n=112)
Total Person-Time (persons-hours)	1194.0	1305.9	1254.6	1277.6	3838.1	5032.1
Ventricular Fibrillation, n (%)	0	0	0	0	0	0
Incidence Rate [a]	---	---	---	---	---	---
Sustained VT, n (%)	0	0	0	0	0	0
Incidence Rate	---	---	---	---	---	---
Non-sustained VT, n (%)	2 (7.7%)	1 (3.6%)	1 (3.4%)	7 (24%)	9 (10%)	11 (10%)
Incidence Rate	0.168	0.077	0.080	0.548	0.234	0.219
High degree AV block, n (%)	0	0	0	2 (6.9%)	2 (2.3%)	2 (1.8%)
Incidence Rate	---	---	---	0.157	0.052	0.040
Atrial Fibrillation, n (%)	1 (3.8%)	0	2 (6.9%)	1 (3.4%)	3 (3.5%)	4 (3.6%)
Incidence Rate	0.084	---	0.159	0.078	0.078	0.080

[a] Incidence rate is defined as the number of patients who experienced an arrhythmia divided by the total person-time within each treatment group

SUPPLEMENTARY TABLE 5. ARRHYTHMIAS OCCURRING BETWEEN 48 HOURS AND 14 DAYS POST-TREATMENT

	Placebo (n=25)	0.5 mg/kg FDY-5301 (n=28)	1.0 mg/kg FDY-5301 (n=28)	2.0 mg/kg FDY-5301 (n=28)	All FDY-5301 (n=84)	Overall (n=109)
Total Person-Time (persons-hours)	6022.9	6317.9	6822.3	6787.3	19927.5	25950.4
Ventricular Fibrillation, n (%)	0	0	0	0	0	0
Incidence Rate	---	---	---	---	---	---
Sustained VT, n (%)	0	0	0	0	0	0
Incidence Rate	---	---	---	---	---	---
Non-sustained VT, n (%)	0	0	1 (3.6%)	0	1 (1.2%)	1 (0.9%)
Incidence Rate	---	---	0.015	---	0.005	0.004
High degree AV block, n (%)	0	0	0	2 (7.1%)	2 (2.4%)	2 (1.8%)
Incidence Rate	---	---	---	0.030	0.010	0.008
Atrial Fibrillation, n (%)	1 (4%)	3 (10.7%)	2 (7.1%)	2 (7.1%)	7 (8.3%)	8 (7.3%)
Incidence Rate	0.017	0.048	0.029	0.030	0.035	0.031

SUPPLEMENTARY TABLE 6. TREATMENT EMERGENT ADVERSE EVENTS

	Placebo (n=29)	0.5 mg/kg FDY-5301 (n=29)	1.0 mg/kg FDY-5301 (n= 31)	2.0 mg/kg FDY-5301 (n= 31)	All FDY-5301 (n=91)	Overall (n=120)
Patients with adverse events	21 (72.4%)	18 (62.1%)	20 (64.5%)	21 (67.7%)	59 (64.8%)	80 (66.7%)
Number of adverse events	61	49	42	30	121	182
Patients with serious adverse events	8 (27.6%) [12]	7 (24.1%) [12]	7 (22.6%) [12]	4 (12.9%) [4]	18 (19.8%) [28]	26 (21.7%) [40]
Patients discontinued due to adverse events	1 (3.4%) [2]	---	---	---	---	1 (0.8%) [2]
Patients with adverse events that resulted in death	1 (3.4%) [1]	---	1 (3.2%) [1]	1 (3.2%) [1]	2 (2.2%) [2]	3 (2.5%) [3]
Patients with cardiac related adverse events	5 (17.2%) [7]	9 (31.0%) [14]	13 (41.9%) [17]	13 (41.9%) [13]	35 (38.5%) [44]	40 (33.3%) [51]
Patients with cardiac related serious adverse events	3 (10.3%) [4]	5 (17.2%) [6]	7 (22.6%) [10]	3 (9.7%) [3]	15 (16.5%) [19]	18 (15.0%) [23]
Patients discontinued due to cardiac related adverse events	1 (3.4%) [2]	---	---	---	---	1 (0.8%) [2]
Patients with cardiac related adverse events that resulted in death	1 (3.4%) [1]	---	1 (3.2%) [1]	1 (3.2%) [1]	2 (2.2%) [2]	3 (2.5%) [3]
Severity (all adverse events)						
Mild	15 (51.7%) [48]	15 (51.7%) [29]	14 (45.2%) [26]	16 (51.6%) [19]	45 (49.5%) [74]	60 (50.0%) [122]
Moderate	7 (24.1%) [11]	8 (27.6%) [15]	7 (22.6%) [8]	5 (16.1%) [9]	20 (22.0%) [32]	27 (22.5%) [43]
Severe	1 (3.4%) [2]	4 (13.8%) [5]	3 (9.7%) [8]	2 (6.5%) [2]	9 (9.9%) [15]	10 (8.3%) [17]
Total	21 (72.4%) [61]	18 (62.1%) [49]	20 (64.5%) [42]	21 (67.7%) [30]	59 (64.8%) [121]	80 (66.7%) [182]

	Placebo (n=29)	0.5 mg/kg FDY-5301 (n=29)	1.0 mg/kg FDY-5301 (n= 31)	2.0 mg/kg FDY-5301 (n= 31)	All FDY-5301 (n=91)	Overall (n=120)
Severity (probable or possible relationship)						
Mild	2 (6.9%) [2]	3 (10.3%) [4]	2 (6.5%) [2]	3 (9.7%) [4]	8 (8.8%) [10]	10 (8.3%) [12]
Moderate	---	---	---	---	---	---
Severe	---	---	---	1 (3.2%) [1]	1 (1.1%) [1]	1 (0.8%) [1]
Total	2 (6.9%) [2]	3 (10.3%) [4]	2 (6.5%) [2]	4 (12.9%) [5]	9 (9.9%) [11]	11 (9.2%) [13]
Relationship to study drug						
Probable	---	---	---	---	---	---
Possible	2 (6.9%) [2]	3 (10.3%) [4]	2 (6.5%) [2]	4 (12.9%) [5]	9 (9.9%) [11]	11 (9.2%) [13]
Unlikely	20 (69.0%) [59]	17 (58.6%) [45]	19 (61.3%) [40]	18 (58.1%) [25]	54 (59.3%) [110]	74 (61.7%) [169]
N = number of patients studied ( ) = percentage of patients with adverse events [ ] = number of adverse events For adverse events that change severity rating, the adverse event will be included only once under the maximum severity rating.						

SUPPLEMENTARY TABLE 7. TREATMENT EMERGENT SERIOUS ADVERSE EVENTS

	Placebo (n=29)	0.5 mg/kg FDY-5301 (n=29)	1.0 mg/kg FDY-5301 (n=31)	2.0 mg/kg FDY-5301 (n = 31)	All FDY-5301 (N = 91)	Overall (N = 120)
Patients with serious adverse events	8 (27.6%)	7 (24.1%)	7 (22.6%)	4 (12.9%)	18 (19.8%)	26 (21.7%)
Number of serious adverse events	12	12	12	4	28	40
Patients discontinued due to serious adverse events	1 (3.4%) [2]	---	---	---	---	1 (0.8%) [2]
Patients with adverse events that resulted in death	1 (3.4%) [1]	---	1 (3.2%) [1]	1 (3.2%) [1]	2 (2.2%) [2]	3 (2.5%) [3]
Patients with cardiac related serious adverse events	3 (10.3%) [4]	5 (17.2%) [6]	7 (22.6%) [10]	3 (9.7%) [3]	15 (16.5%) [19]	18 (15.0%) [23]
Patients discontinued due to cardiac related serious adverse events	1 (3.4%) [2]	---	---	---	---	1 (0.8%) [2]
Patients with cardiac related adverse events that resulted in death	1 (3.4%) [1]	---	1 (3.2%) [1]	1 (3.2%) [1]	2 (2.2%) [2]	3 (2.5%) [3]

	Placebo (n=29)	0.5 mg/kg FDY-5301 (n=29)	1.0 mg/kg FDY-5301 (n=31)	2.0 mg/kg FDY-5301 (n = 31)	All FDY-5301 (N = 91)	Overall (N = 120)
Severity (all serious adverse events)						
Mild	3 (10.3%) [4]	---	3 (9.7%) [3]	1 (3.2%) [1]	4 (4.4%) [4]	7 (5.8%) [8]
Moderate	5 (17.2%) [6]	5 (17.2%) [7]	2 (6.5%) [2]	2 (6.5%) [2]	9 (9.9%) [11]	14 (11.7%) [17]
Severe	1 (3.4%) [2]	4 (13.8%) [5]	2 (6.5%) [7]	1 (3.2%) [1]	7 (7.7%) [13]	8 (6.7%) [15]
Total	8 (27.6%) [12]	7 (24.1%) [12]	7 (22.6%) [12]	4 (12.9%) [4]	18 (19.8%) [28]	26 (21.7%) [40]
Severity (probable or possible relationship)						
Mild	---	---	---	---	---	---
Moderate	---	---	---	---	---	---
Severe	---	---	---	---	---	---
Total	---	---	---	---	---	---

	Placebo (n=29)	0.5 mg/kg FDY-5301 (n=29)	1.0 mg/kg FDY-5301 (n=31)	2.0 mg/kg FDY-5301 (n = 31)	All FDY-5301 (N = 91)	Overall (N = 120)
Relationship to study drug						
Probable	---	---	---	---	---	---
Possible	---	---	---	---	---	---
Unlikely	8 (27.6%) [12]	7 (24.1%) [12]	7 (22.6%) [12]	4 (12.9%) [4]	18 (19.8%) [28]	26 (21.7%) [40]

n = number of patients studied ( ) = percentage of patients with adverse events [ ] = number of adverse events
For adverse events that change severity rating, the adverse event will be included only once under the maximum severity rating.

SUPPLEMENTARY TABLE 8. DEATHS AND HEART FAILURE HOSPITALIZATIONS OUT TO 6 MONTHS

	Placebo (N=29)	0.5 mg/kg FDY-5301 (N=29)	1.0 mg/kg 2.0 FDY-5301 (N=31)	3.0 mg/kg 4.0 FDY-5301 (N=31)	All FDY-5301 (N=91)
Overall Total	2 (6.9%) [2]	--	1 (3.2%) [3]	1 (3.2%) [1]	2 (2.2%) [4]
Death	1 (3.4%) [1]	--	1 (3.2%) [1]	1 (3.2%) [1]	2 (2.2%) [2]
Cardiac Failure Hospitalizations	1 (3.4%) [1]	--	1 (3.2%) [2]	--	1 (1.1%) [2]

Number of Patients in Each Treatment Group Affected (% of Treatment Group) [Number of Events]

SUPPLEMENTARY TABLE 9. FINAL INFARCT SIZE- 3 MONTHS POST-TREATMENT

3 Months Post-Treatment	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
IS/LV (%)	mean	16.5	15.9	14.8	12.3	14.3
	SD	12.71	15.82	13.89	12.81	14.18
	median	14.9	11.7	11.4	8.5	11.1
	Min	0.0	0.0	0.0	0.0	0.0
	Max	48.4	52.0	50.7	49.5	52.0
	N	15	24	14	22	60

SUPPLEMENTARY TABLE 10. INFARCT SIZE, CHANGE OVER BASELINE MEASUREMENTS AT 3 MONTHS POST-TREATMENT

Change from BL[a] At 3 months	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
IS/LV (%)	mean	-4.5	-6.0	-5.5	-8.2	-6.6
	SD	7.15	9.18	6.40	9.53	8.60
	median	-3.1	-4.6	-5.1	-6.8	-5.1
	min	-14.1	-32.8	-24.0	-36.5	-36.5
	max	13.7	7.8	3.4	4.8	7.8
	n (paired)	15	21	14	19	54

[a] Baseline (BL) = measurement at 72-hour time point (data not shown)

SUPPLEMENTARY TABLE 11. FINAL INFARCT SIZE AT THREE-MONTHS POST-TREATMENT IN PATIENTS WITH ANTERIOR STEMI

3 Months Post-Treatment	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
IS/LV (%)	mean	20.6	19.5	16.4	11.6	16.4
	SD	17.55	14.08	17.66	11.58	14.17
	median	22.8	19.7	10.4	9.3	14.4
	min	1.4	0.0	0.0	0.0	0.0
	max	48.4	52.0	50.7	34.4	52.0
	n	6	11	6	7	24

SUPPLEMENTARY TABLE 12. INFARCT SIZE, CHANGE OVER BASELINE MEASUREMENTS AT 3 MONTHS POST-TREATMENT IN PATIENTS WITH ANTERIOR STEMI

Change from BL[a] At 3 months	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
IS/LV (%)	mean	-6.5	-8.2	-2.4	-10.3	-7.3
	SD	10.21	7.03	3.99	13.11	9.05
	median	-10.1	-8.5	-2.5	-9.7	-5.4
	min	-14.1	-18.7	-6.8	-36.5	-36.5
	max	13.7	0.5	3.4	4.8	4.8
	n (paired)	6	9	6	7	22

[a] Baseline (BL) = measurement at 72-hour time point

SUPPLEMENTARY 13. FINAL INFARCT SIZE AT 3 MONTHS POST-TREATMENT IN PATIENTS WITH TIMI 0-1 AT ADMISSION

3 Months Post-Treatment	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
IS/LV (%)	mean	17.6	15.5	16.8	12.8	14.6
	SD	12.51	14.89	14.97	12.92	13.89
	median	16.3	12.0	14.2	9.3	11.8
	min	0.0	0.0	0.0	0.0	0.0
	max	48.4	51.0	50.7	49.5	51.0
	n	14	17	11	21	49

SUPPLEMENTARY TABLE 14. INFARCT SIZE, CHANGE OVER BASELINE MEASUREMENTS AT 3 MONTHS POST-TREATMENT IN PATIENTS WITH TIMI 0-1 AT ADMISSION

Change from BL[a] At 3 months	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
IS/LV (%)	mean	-3.8	-6.5	-6.4	-8.1	-7.1
	SD	6.88	9.91	6.66	9.80	8.99
	median	-2.5	-4.6	-5.7	-5.5	-5.4
	min	-13.0	-32.8	-24	-36.5	-36.5
	max	13.7	7.8	0.0	4.8	7.8
	n (paired)	14	15	11	18	44

[a] Baseline (BL) = measurement at 72-hour time point

SUPPLEMENTARY TABLE 15. FINAL INFARCT SIZE BY CATEGORY IN ALL PATIENTS TREATED WITH PLACEBO OR FDY-5301

	n			Odds Ratio
Treatment	No or Small Infarcts	Large Infarcts	Comparison	and 95% CI (%)
Placebo	9	6	---	---
0.5 mg/kg FDY-5301	16	8	0.5 mg/kg FDY-5301 vs Placebo	75.0 (19.7, 285.5)
1.0 mg/kg FDY-5301	11	3	1.0 mg/kg FDY-5301 vs Placebo	40.9 (7.9, 211.4)
2.0 mg/kg FDY-5301	17	5	2.0 mg/kg FDY-5301 vs Placebo	44.1 (10.5, 185.4)
All FDY-5301	44	16	All FDY-5301 vs Placebo	54.5 (16.7, 177.7)

CI = confidence interval; n = number of patients
Odds ratio and its confidence intervals were derived based on the ratio of the number of patients who had large infarcts (≥19% of LV) versus the number of patients who had no or small infarcts within each FDY 5301 group (and overall) against the placebo group.

SUPPLEMENTARY TABLE 16. FINAL INFARCT SIZE BY CATEGORY IN PATIENTS WITH ANTERIOR STEMI

	n			Odds Ratio
Treatment	No or Small Infarcts	Other Infarcts	Comparison	and 95% CI (%)
Placebo	2	4	---	---
0.5 mg/kg FDY-5301	5	6	0.5 mg/kg FDY-5301 vs Placebo	60.0 (7.6, 476.0)
1.0 mg/kg FDY-5301	5	1	1.0 mg/kg FDY-5301 vs Placebo	10.0 (0.6, 154.4)
2.0 mg/kg FDY-5301	6	1	2.0 mg/kg FDY-5301 vs Placebo	8.3 (0.6, 125.7)
All FDY-5301	16	8	All FDY-5301 vs Placebo	25.0 (3.7, 166.8)

CI = confidence interval; n = number of patients

Odds ratio and its confidence intervals were derived based on the ratio of the number of patients who had other infarcts versus the number of patients who had no or small infarcts within each FDY-5301 group (and overall) against the placebo group.

SUPPLEMENTARY TABLE 17. FINAL INFARCT SIZE BY CATEGORY IN PATIENTS WITH TIMI 0-1 AT ADMISSION

	n			
Treatment	No or Small Infarcts	Large Infarcts	Comparison	Odds Ratio, 95% CI (%)
Placebo	8	6	---	---
0.5 mg/kg FDY-5301	12	5	0.5 mg/kg FDY-5301 vs Placebo	55.6 (12.6, 245.6)
1.0 mg/kg FDY-5301	8	3	1.0 mg/kg FDY-5301 vs Placebo	50.0 (9.2, 273.0)
2.0 mg/kg FDY-5301	16	5	2.0 mg/kg FDY-5301 vs Placebo	41.7 (9.7, 179.2)
All FDY-5301	36	13	All FDY-5301 vs Placebo	48.1 (14.0, 165.4)

CI = confidence interval; n = number of patients

Odds ratio and its confidence intervals were derived based on the ratio of the number of patients who had large infarcts (≥19% of LV) versus the number of patients who had no or small infarcts within each FDY-5301 group (and overall) against the placebo group.

SUPPLEMENTARY TABLE 18. MEASURES OF CARDIAC FUNCTION AT 3 MONTHS POST-TREATMENT

3 Months Post-Treatment	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
LV EDVi ($mL/kg/m^2$)	mean	80.2	78.7	73.3	77.5	76.9
	SD	16.82	20.32	22.24	32.11	25.37
	median	75.0	78.0	63.5	73.0	73.0
	n	17	24	16	23	63
LV ESVi ($mL/kg/m^2$)	mean	37.6	35.6	32.6	29.7	32.7
	SD	14.86	17.21	21.99	13.97	17.40
	median	36.0	29.0	25.5	27.0	28.0
	n	17	24	16	23	63
LVEF (%)	mean	55.9	56.7	58.1	60.4	58.4
	SD	11.55	11.10	14.27	9.31	11.33
	median	53.9	59.5	58.9	63.2	59.8
	n	17	24	16	23	63

SUPPLEMENTARY TABLE 19. MEASURES OF CARDIAC FUNCTION AT 3 MONTHS POST-TREATMENT IN PATIENTS WITH ANTERIOR STEMI

3 Months Post-Treatment	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
LV EDVi	mean	82.1	84.9	64	65.1	73.6
(mL/kg/m2)	SD	16.91	16.91	9.63	14.71	17.53
	median	75	85	61	64.5	72
	n	7	11	6	8	25
LV ESVi	mean	41.1	38.7	27.3	23.5	31.1
(mL/kg/m2)	SD	15.78	15.72	12.11	8.18	14.23
	median	36	37	28	23.5	28
	n	7	11	6	8	25
LVEF (%)	mean	54.9	56	58.7	64.2	59.2
	SD	13.89	11.23	15.5	8.43	11.68
	median	50.4	55.7	57.2	67.6	59.8
	n	7	11	6	8	25

SUPPLEMENTARY TABLE 20. MEASURES OF CARDIAC FUNCTION AT 3 MONTHS POST-TREATMENT IN PATIENTS WITH TIMI 0-1 AT ADMISSION

3 Months Post-Treatment	Statistic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
LV EDVi	mean	81.9	77.3	75.2	78.1	77.1
(mL/kg/m^2)	SD	17.16	22.33	24.12	32.73	27.12
	median	77.0	76.0	66.0	73.0	72.5
	n	15	17	13	22	52
LV ESVi	mean	39.4	35.9	33.8	30.3	33.0
(mL/kg/m^2)	SD	14.83	19.18	24.26	14.05	18.48
	median	36.0	29.0	26.0	27.0	27.5
	n	15	17	13	22	52
LVEF (%)	mean	54.9	56.0	58.2	59.8	58.2
	SD	11.72	12.15	15.20	9.16	11.75
	median	53.5	58.6	59.7	63.0	59.8
	n	15	17	13	22	52

SUPPLEMENTARY TABLE 21. PROPORTION OF PATIENTS WITH ST-SEGMENT RESOLUTION AT 4 HOURS POST-TREATMENT

	n/N	Comparison	Odds Ratio and 95% CI (%)
Placebo	9/19	---	---
0.5 mg/kg FDY-5301	12/25	0.5 mg/kg FDY-5301 vs Placebo	102.6 (31.1, 338.6)
1.0 mg/kg FDY-5301	17/25	1.0 mg/kg FDY-5301 vs Placebo	236.1 (68.9, 809.2)
2.0 mg/kg FDY-5301	11/21	2.0 mg/kg FDY-5301 vs Placebo	122.2 (35.3, 423.5)
All FDY-5301	40/71	All FDY-5301 vs Placebo	143.4 (51.9, 395.7)

CI = confidence interval; n = number of patients with ST-segment resolution; N = total number of patients
Odds ratio and its confidence intervals were derived based on the ratio of the number of patients who experienced ST-segment resolution versus the number of patients who did not experience ST-segment resolution within each FDY-5301 group (and overall) against the placebo group.

SUPPLEMENTARY TABLE 22. SERUM TROPONIN CONCENTRATIONS OVER THE FIRST 48 HOURS POST-TREATMENT

	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301
Adjusted Troponin $AUC_{0\text{-}48}$ (h*µg/L)				
arithmetic mean	172	121	137	155
arithmetic SD	184	109	142	137
median	112	90.5	98.1	108
min	4.50	-19.3	0.0274	32.8
max	752	383	538	591
n	19	25	25	24

Adjusted refers to adjusted for baseline, where AUC is calculated on change from baseline concentrations.
Baseline is the most recent value measured prior to study drug dosing.

SUPPLEMENTARY TABLE 23. SERUM TROPONIN CONCENTRATIONS OVER THE FIRST 48 HOURS POST-TREATMENT IN PATIENTS WITH ANTERIOR STEMI

	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301
Adjusted Troponin $AUC_{0\text{-}48,}$ (h*µg/L)				
arithmetic mean	230	129	139	199
arithmetic SD	273	107	180	200
median	83.8	123	55.0	111
min	42.5	-19.3	0.0274	32.8
max	752	361	538	591
n	8	12	9	9

Adjusted refers to adjusted for baseline, where AUC is calculated on change from baseline concentrations.
Baseline is the most recent value measured prior to study drug dosing

SUPPLEMENTARY TABLE 24. SERUM TROPONIN CONCENTRATIONS OVER THE FIRST 48 HOURS POST-TREATMENT IN PATIENTS WITH TIMI 0-1 AT ADMISSION

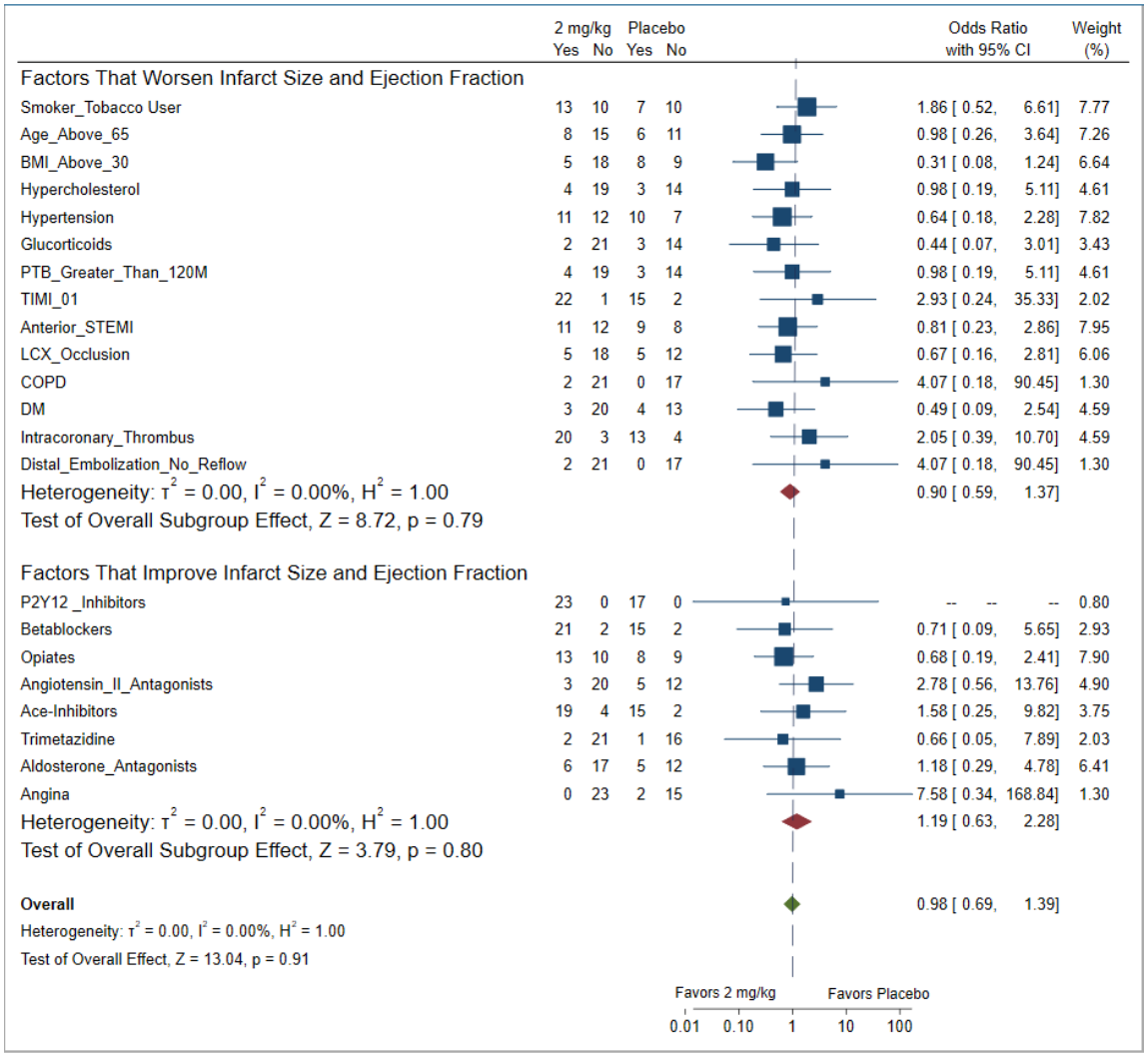
	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301
Adjusted Troponin $AUC_{0\text{-}48,}$ (h*µg/L)				
arithmetic mean	179	132	151	160
arithmetic SD	187	114	146	138
median	119	90.5	101	109
min	4.50	0.388	0.0274	32.8
max	752	383	538	591
n	18	19	22	23

Adjusted refers to adjusted for baseline, where AUC is calculated on change from baseline concentrations.
Baseline is the most recent value measured prior to study drug dosing

SUPPLEMENTARY TABLE 25. DICHOTOMIZED BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS ON PATIENTS COMPLETING FOLLOW-UP CMR

	2 mg/kg FDY-5301 (n=23)	Placebo (n=17)	P value
Peri-Procedural Medications			
P2Y12 Inhibitors	23	17	1.00
Beta Blockers	21	15	0.75
Opioids	13	8	0.55
Angiotensin II Antagonists	3	5	0.20
ACE Inhibitors	19	15	0.62
Trimetazidine	2	1	0.74
Aldosterone Antagonists	6	5	0.82
Glucorticoids	2	3	0.40
Demographics			
Smoke/Tobacco Use	13	7	0.34
Age > 65	8	6	0.97
BMI > 30	5	8	0.09
Comorbidities			
Angina	0	2	0.09
Hypercholesterolemia	4	3	0.98
Hypertension	11	10	0.49
COPD	2	0	0.21
DM	3	4	0.39
PCI Related Characteristics			
PTB > 120 Min.	4	3	0.98
TIMI 0/1 at Admission	22	15	0.38
LAD Artery Occlusion	11	9	0.75
LCX Artery Occlusion	5	5	0.58
Intracoronary Thrombus	20	13	0.39
Distal Embolization and/or No Reflow	2	0	0.21

SUPPLEMENTARY TABLE 26. FOREST PLOT OF PERTINENT DICHOTOMOUS VARIABLES WITH ESTABLISHED DIRECTION OF EFFECT



Supplementary References

[1] Sahan KM, Channon KM, Choudhury RP, Kharbanda RK, Lee R, Sheehan M. Refining the Enrolment Process in Emergency Medicine Research. Eur J Cardiovasc Med. 2016;4:506-10.
[2] Stankovic S, Asanin M, Trifunovic D, Majkic-Singh N, Ignjatovic S, Mrdovic I, et al. Time-dependent changes of myeloperoxidase in relation to in-hospital mortality in patients with the first anterior ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention. Clin Biochem. 2012;45:547-51.
[3] Andrassy M, Volz HC, Riedle N, Gitsioudis G, Seidel C, Laohachewin D, et al. HMGB1 as a predictor of infarct transmurality and functional recovery in patients with myocardial infarction. J Intern Med. 2011;270:245-53.
[4] Sorensen MV, Pedersen S, Mogelvang R, Skov-Jensen J, Flyvbjerg A. Plasma high-mobility group box 1 levels predict mortality after ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2011;4:281-6.
[5] Sedláková E, Rácz O, Lovásová E, Beòaèka R, Kurpas M, Chmelárová A, et al. Markers of oxidative stress in acute myocardial infarction treated by percutaneous coronary intervention. Central European Journal of Medicine. 2009;4:26-31.
[6] Fontes JA, Rose NR, Cihakova D. The varying faces of IL-6: From cardiac protection to cardiac failure. Cytokine. 2015;74:62-8.
[7] Rakhit RD, Seiler C, Wustmann K, Zbinden S, Windecker S, Meier B, et al. Tumour necrosis factor-alpha and interleukin-6 release during primary percutaneous coronary intervention for acute myocardial infarction is related to coronary collateral flow. Coron Artery Dis. 2005;16:147-52.
[8] Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsumura T, et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation. 1993;88:82-91.
[9] Fonseca C, Sarmento PM, Minez A, Goncalves E, Covas R, Dias AR, et al. Comparative value of BNP and NT-proBNP in diagnosis of heart failure. Rev Port Cardiol. 2004;23:979-91.
[10] Asakawa H, Nishikimi T, Suzuki T, Hara S, Tsubokou Y, Yagi H, et al. Elevation of two molecular forms of adrenomedullin in plasma and urine in patients with acute myocardial infarction treated with early coronary angioplasty. Clin Sci (Lond). 2001;100:117-26.
[11] Ng LL, Sandhu JK, Narayan H, Quinn PA, Squire IB, Davies JE, et al. Proenkephalin and prognosis after acute myocardial infarction. J Am Coll Cardiol. 2014;63:280-9.
[12] Phatharajaree W, Phrommintikul A, Chattipakorn N. Matrix metalloproteinases and myocardial infarction. Can J Cardiol. 2007;23:727-33.
[13] Furenes EB, Arnesen H, Solheim S, Grogaard HK, Hoffmann P, Seljeflot I. The profile of circulating metalloproteinases after PCI in patients with acute myocardial infarction or stable angina. Thromb Res. 2009;124:560-4.
[14] Ding S, Liu H, Lu Q, Gong Z, Jiang J, Chen Z, et al. Changes of matrix metalloproteinase-9 and tissue inhibitors of metalloproteinase-1 during left ventricular remodeling in acute myocardial infarction patients after percutaneous coronary intervention. Biomedical Research. 2013;24:179-84.
[15] Siebenhofer A, Ng LL, Plank J, Berghold A, Hodl R, Pieber TR. Plasma N-terminal pro-brain natriuretic peptide in Type 1 diabetic patients with and without diabetic nephropathy. Diabet Med. 2003;20:535-9.
[16] Stiermaier T, Jobs A, de Waha S, Fuernau G, Poss J, Desch S, et al. Optimized Prognosis Assessment in ST-Segment-Elevation Myocardial Infarction Using a Cardiac Magnetic Resonance Imaging Risk Score. Circ Cardiovasc Imaging. 2017;10.
[17] Festic E, Rawal B, Gajic O. How to improve assessment of balance in baseline characteristics of clinical trial participants-example from PROSEVA trial data? Ann Transl Med. 2016;4:79.