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

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Abstract

Background: Ischemia-reperfusion injury remains a major clinical problem in patients with ST-elevation myocardial infarction (STEMI), leading to myocardial damage, ventricular arrhythmias and heart failure, despite early reperfusion by primary percutaneous coronary intervention (PPCI). There are no effective therapies to limit ischemia-reperfusion injury, which is caused by multiple pathways activated by rapid tissue reoxygenation and the generation of reactive oxygen species (ROS).

FDY-5301 contains sodium iodide, an inorganic halide, ubiquitous in biological systems at low-levels, and is an elemental reducing agent that at high concentrations acts as a catalytic anti-peroxidant in the chemical detoxification of hydrogen peroxide. We sought to test the feasibility, safety and potential utility of FDY-5301 as a treatment to limit ischemia-reperfusion injury, in the emergency setting, in patients with first-time STEMI undergoing PPCI.

Methods: STEMI patients (n=120, median 62 years) presenting within 12h of chest pain onset were randomized at 20 PPCI centers, in a double blind Phase 2 clinical trial, to receive FDY-5301 (0.5, 1.0 or 2.0 mg/kg) or placebo prior to reperfusion, to evaluate the feasibility endpoints. Participants underwent continuous ECG monitoring for 14 days after PPCI to address pre-specified cardiac arrhythmia safety end points and cardiac magnetic resonance imaging (MRI) at 72 hours and at 3 months to assess exploratory efficacy end points.

Results: Intravenous FDY-5301 was delivered before re-opening of the infarct-related artery in 97% participants and increased plasma iodide levels ~1000-fold within 2 minutes. There was no significant increase in the primary safety end point of incidence of cardiac arrhythmias of concern. MRI at 3 months revealed median final infarct sizes of 14.9% in placebo-treated patients compared with 8.5% in patients receiving 2.0mg/kg FDY-5301, with LV ejection fractions of 53.9% vs. 63.2%, respectively, although the study was not powered to detect statistical significance. FDY-5301 treatment reduced the likelihood of a large (>19% LV mass) final infarct by 56% compared with placebo and significantly improved the end-systolic volume index in anterior STEMI (41.1 vs 31.1 ml/kg/m^2, $p<0.05$). In patients receiving FDY-5301,

there was a significant reduction in the levels of MPO, MMP2 and NTproBNP after PPCI, but no reduction with placebo.

Conclusions: Intravenous FDY-5301, delivered immediately prior to PPCI in acute STEMI, is feasible, safe, and shows potential efficacy. A larger trial is justified to test the effects of FDY-5301 on acute ischemia-reperfusion injury and clinical outcomes.

Clinical Trial Registration: CT.gov NCT03470441; EudraCT 2017-000047-41

Introduction

Acute ST segment elevation myocardial infarction (STEMI) is a leading cause of cardiovascular death and the primary cause of chronic heart failure. Primary percutaneous coronary intervention (PPCI) reduces infarct size. However, rapid reperfusion of the ischemic myocardium causes further damage due to ischemia-reperfusion injury, associated with a burst of reactive oxygen species (ROS) production, leading to increased infarct size, arrhythmias and heart failure [1]. Many experimental therapies targeting myocardial ischemia-reperfusion injury in STEMI have been tested, but no treatments have yet entered clinical practice [2]. An effective therapy must act rapidly and have a rapid onset pharamacokinetic profile as ischemia-reperfusion injury is precipitated immediately on reopening the occluded coronary artery. Ensuring timely and consistent delivery without delay to the reopening of the culprit vessel therefore poses major logistic challenges in the emergency setting of PPCI.

Iodides are reduced iodine anions that have a biological role in thyroid function, but also exert catalytic ROS-inactivating effects as elemental reducing agents (ERAs). Iodine is an essential nutrient for humans and is ubiquitous in biological systems [3, 4].

We have recently shown that sodium iodide can act as an anti-peroxidant in preclinical experimental models of ischemia-reperfusion, leading to a reduction in acute myocardial injury.[5, 6] Iodide treatment reduced myocardial neutrophil content, reduced infarct size and improved LV function, whereas the oxidized iodine anion, iodate (IO_3^-), had no beneficial effect. Iodide also plays roles in modulating inflammation. Administration of iodide markedly decreased neutrophil migration in Boyden chamber assays,[7] and inhibited neutrophil activation, leading to reductions in hydroxyl radical and hydrogen peroxide release.[8] FDY-5301 is a formulation of sodium iodide for human intravenous administration, that is well tolerated without signs of toxicity at doses of up to 10 mg/kg in healthy volunteers.

We sought to address the hypotheses that administration of FDY-5301 as a single dose bolus of either 0.5 mg/kg FDY-5301 (n = 20), 1.0 mg/kg FDY-5301 (n = 20), 2.0 mg/kg FDY-5301 (n=20) or placebo (n

=20) in patients undergoing PPCI for STEMI is safe, primarily as determined by 14 days of monitoring for malignant arrhythmias. To achieve this we performed a randomized, double-blind, placebo-controlled phase 2 safety dose-ranging study of FDY-5301 in first-time STEMI patients presenting as an emergency for PPCI.

Although this study was not powered to assess clinical efficacy, we further sought to explore any preliminary signal through the quantification of left ventricular function and myocardial infarct size by magnetic resonance imaging, as well as assessing biomarkers of inflammation, myocardial injury and infarction. Finally, we sought to investigate the pharmacokinetics of FDY-5301 administered in this diseased population to assess exposures in comparison to that demonstrated in Healthy Volunteers.

Methods

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.

Full details are provided in the Supplementary Materials and Methods.

Results

Study patients

Patients (n=120) presenting with a first STEMI within 12 hours of chest pain onset were enrolled at centers in the United Kingdom (n=64), Poland (n=20), Hungary (n=30) and the United States (n=6). Patient characteristics are summarized in Table 1. The median age of study participants was 62 (range 36–79) years. More men than women were enrolled (n=83 *vs* n=37, respectively) and the majority of patients were white compared with other races (n=113 *vs* n=7, respectively). The median pain-to-

balloon time was 220 minutes, with no statistically significant differences between the treatment groups.

Of 120 patients randomized to receive placebo or FDY-5301, two died before the arrhythmia sensors were applied and five patients declined consent to continue participation in the study, leaving 113 patients. Patient disposition across the treatment groups is summarized in Supplementary Table 1. Despite initial symptoms and ECG changes suggesting STEMI at presentation, 5 of 113 patients were subsequently found to have Takotsubo cardiomyopathy rather than myocardial infarction but are included in the analysis of arrhythmias since they were treated with placebo or FDY-5301, but did not undergo follow-up CMR. CMR scans taken three months post-treatment with measures of cardiac function were obtained from 80 patients with final infarct size data available from 75 patients. Attrition was due to withdrawal of consent from the study in general or specifically from CMR from 19 patients (mostly due to claustrophobia), Takotsubo cardiomyopathy in 5 patients (as above) and technical difficulties with scan acquisition in 10 patients (for cardiac function parameters) and 15 patients (for infarct size parameters) and a contraindication in 6 patients (Supplementary Table 2).

Pharmacokinetic Profile and Tolerance of FDY-5301 in STEMI Patients Undergoing PPCI

Plasma iodide concentrations were measured pre-dose and at two-minutes, one hour, four hours, 24 hours and 48 hours after the bolus administration of FDY-5301 at doses of either 0.5. 1.0 or 2.0 mg/kg. The median (75-25 centile) time of dose administration prior to PCI of the infarct-related artery was 10 (range 19-6) minutes. The bolus injection of FDY-5301 was completed before the passage of the coronary guidewire in 104 out of 107 (97%) of patients. FDY-5301 administration increased plasma iodide concentration at 2 minutes by ~1,000-fold compared with placebo (Figure 1), which is comparable to preclinical rat and Phase 1 human findings (Supplementary Figure 1). Pharmacokinetic modeling indicated a half-life of plasma iodide concentration of approximately 12 to 16 hours after FDY-5301 administration (Supplementary Table 3).

Incidence of Cardiac Arrhythmias During the First 14 Days After FDY-5301 Treatment

The primary endpoint was the combined number and incidence of clinically important arrhythmias that occurred in each treatment group over a 14-day period post-study drug.

Arrhythmia data are presented in the first 48 hours post-treatment (Supplementary Table 4) and those occurring between 48 hours and 14 days post-treatment (Supplementary Table 5).

In the first 48 hours following PPCI, no episodes of ventricular fibrillation nor sustained ventricular tachycardia were recorded in any treatment group. Two patients in the placebo group (7.7%), one patient in the 0.5 mg/kg FDY-5301 group (3.6%), one patient in the 1.0 mg/kg FDY-5301 group (3.4%), and seven patients in the 2.0 mg/kg FDY-5301 group (24%) experienced at least one episode of non-sustained ventricular tachycardia during the initial 48 hours post-treatment. Also, during the initial 48 hours post-treatment, two patients in the 2.0 mg/kg FDY-5301 treatment group (6.9%) experienced at least one self-limiting episode of high-degree AV Block (both second degree, Mobitz 1) while no episodes of high degree AV block were recorded in any of the other treatment groups. One patient in the placebo group (3.8%), two patients in the 1.0 mg/kg FDY-5301 group (6.9%) and one patient in the 2.0 mg/kg FDY-5301 group (3.4%) experienced at least one episode of self-limiting atrial fibrillation.

In the time interval spanning 48 hours to 14 days post-treatment, no ventricular fibrillation or sustained ventricular tachycardia were recorded in any treatment group. One patient in the 1.0 mg/kg FDY-5301 group (3.6%) experienced at least one episode of non-sustained ventricular tachycardia while no episodes of non-sustained ventricular tachycardia were recorded in any of the other treatment groups. Two patients in the 2.0 mg/kg FDY-5301 treatment group (7.1%) experienced at least one transient episode of high-degree AV Block while no episodes of high degree AV block were recorded in any of the other treatment groups. One patient in the placebo group (4%), three patients in the 0.5 mg/kg FDY-5301 group (10.7%), two patients in the 1.0 mg/kg FDY-5301 group (7.1%), and

two patients in the 2.0 mg/kg FDY-5301 group (7.1%) experienced at least one episode of atrial fibrillation.

Clinical Safety

Adverse events (AEs) and serious adverse events (SAEs) observed in placebo and FDY-5301-treated patients are summarized in Supplementary Table 6 and Supplementary Table 7, respectively. Forty SAEs were reported in 26 of the 120 patients randomized. The total number of deaths and hospitalizations due to heart failure out to 6 months are shown in Supplementary Table 8. The cardiac and non-cardiac SAEs were all reviewed by an un-blinded cardiologist and none were considered to be related to study drug and were consistent with normally expected post STEMI events in this population.

There were no significant changes in plasma T3, T4 or TSH levels after administration of FDY-5301 at any dose, either in the 48 hours following administration or at 3 months (Supplementary Figure 2).

Effects of FDY-5301 on Infarct Size Quantified by Cardiac MRI

CMR at three months after PPCI showed median final infarct size of 14.9% of the ventricular volume in placebo-treated patients compared with 11.7%, 11.4% and 8.5% in FDY-5301 treated patients at doses of 0.5 mg/kg, 1.0 mg/kg and 2.0 m/kg, respectively (Figure 2). These translate into relative reductions of 21.5%, 23.5% and 43% when comparing 0.5 mg/kg, 1.0 mg/kg and 2.0 mg/kg FDY-5301 respectively with placebo across all patients. When comparing final median infarct size in patients treated with any dose of FDY-5301 versus placebo, we observed an absolute reduction of 3.8% (from 14.9% placebo to 11.1% all FDY-5301), corresponding to a relative reduction in infarct size of 25.6% (Supplementary Table 9). These differences in median infarct size were not statistically significant when analyzed by Kruskal-Wallis and Dunn's post-test separately comparing the mean ranks of each

FDY-5301 treatment group to placebo (p>0.99, p>0.99, p=0.63 respectively). Results were similar when infarct size (IS) was expressed as mass (g) instead of IS/LV (data not shown).

Change from "baseline" infarct size was calculated in each treatment group using infarct size data from the 72-hour scan as the baseline by which the final 3-month infarct size data was compared. Only patients who underwent CMR scans at both time points were included in this analysis (n=69).

In the placebo group, infarct size was reduced by an average of 4.5% at three months post-treatment compared to baseline measurements. In patients treated with 0.5 mg/kg, 1.0 mg/kg or 2.0 mg/kg FDY-5301, final infarct size at three months was reduced 6.0%, 5.5%, and 8.2% over baseline in each treatment group, respectively. In patients treated with any dose of FDY-5301, final infarct size at 3 months was reduced by 6.6% over baseline measurements (Supplementary Table 10). Results were similar when infarct size was expressed as mass (g) instead of IS/LV (data not shown).

Final infarct sizes and change in infarct over baseline for patients presenting with anterior STEMI (n=30) are shown in Supplementary Tables 11 and 12, for patients with TIMI 0-1 flow at admission (n=63) in Supplementary Tables 13 and 14.

In a categorical analysis of final infarct size, based on a previously reported ROC analysis of prognostic factors after STEMI,[23] we calculated the proportion of patients in each treatment group who had a final infarct size that was ≥19% LV at three months post-treatment. Odds ratios and 95% confidence intervals were derived based on the ratio of the number of patients with large infarcts (≥19% LV) vs. small infarcts (<19% LV) within each FDY-5301 treatment group (and overall) vs. placebo.

Compared with placebo, the odds of having a final infarct size of ≥19% LV at three months post-treatment were 25% less, 59% less and 56% less in all patients treated with 0.5 mg/kg, 1.0 mg/kg or 2.0 mg/kg FDY-5301, respectively. The odds of having a final infarct size of ≥19% LV at three months post-treatment in patients treated with any dose of FDY-5301 were 45% less than patients treated

with placebo (Supplementary Table 15). Data for patients with anterior STEMI and TIMI 0-1 flow are shown in Supplementary Tables 16 and 17.

Effects of FDY-5301 on LV Function after STEMI, Quantified by CMR

Of the 120 patients enrolled in the study, we obtained EDVi, ESVi, and LVEF data from CMR scans taken three months post-treatment from 80 patients. The distribution by treatment of patients who did not undergo CMR is shown in Supplementary Table 2. Lower ESVi and EDVi compared to placebo reflect improved cardiac function in patients treated with FDY-5301. In patients treated with placebo, final mean LVEF was 55.9% and was increased to 56.7%, 58.1% and 60.4% with FDY-5301 treatment at doses of 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively. In patients treated with any dose of FDY-5301, LVEF was 58.4% (Supplementary Table 18). In patients presenting with anterior STEMI and in those with TIMI 0 or 1 flow there were larger improvements in cardiac function at three months compared with baseline (Supplementary Tables 19 and 20, respectively).

Effects of FDY-5301 on ECG ST-Segment Resolution and Cardiac Biomarker Release

We calculated the proportion of patients in each treatment group with ST-segment resolution defined as 50% reduction in ST segment elevation at 4 hours post-treatment compared to baseline. Compared with placebo, the odds of experiencing ST-segment resolution were 2.6% higher in patients treated with 0.5 mg/kg FDY-5301, 136.1% higher in patients treated with 1.0 mg/kg FDY-5301, and 22.2% higher in patients treated with 2.0 mg/kg FDY-5301. The odds of experiencing ST-segment resolution in patients treated with any dose of FDY-5301 were 43.4% higher than patients treated with placebo (Supplementary Table 21).

The troponin $AUC_{0\text{-}48}$ were derived from the serum levels of troponin collected pre-dose, 12, 24 and 48 hours post-treatment. In patients treated with placebo, the mean serum troponin concentration

(AUC_{0-48}) was 172 h*µg/L compared with 121, 137 and 155 h*µg/L in patients treated with 0.5 mg/kg, 1.0 mg/kg and 2.0 mg/kg respectively (Supplementary Table 22). No statistically significant differences in serum troponin concentrations were observed using a one-way ANOVA and Dunnett's post-test separately comparing each FDY-5301 treatment group to placebo (p=0.56, 0.86, 0.95 respectively). Data for patients with anterior STEMI and those with TIMI 0 or 1 flow are shown in Supplementary Tables 23 and 24.

We also measured plasma biomarkers related to acute cardiac dysfunction, myocardial remodeling and inflammation (NT-proBNP, MMP-2 and MPO, respectively), comparing the change in these biomarkers after administration of either FDY-5301 or placebo. The levels of MMP-2 and MPO did not change significantly with placebo administration, however the levels of MPO (at 4 hours) and MMP-2 (at 48 hours) were significantly reduced from baseline following administration of FDY-5301. Furthermore, there was a reduction in NT-proBNP between 24 hours and 48 hours for patients receiving FDY-5301 (Figure 3).

Exploring the Impact of Potential Confounding Variables

Dichotomized baseline demographic and clinical characteristics with a reported impact on infarct size and ejection fraction in preclinical and/or clinical studies are shown in Supplementary Table 25 for the 2 mg/kg FDY-5301 and placebo groups. To illustrate the aggregate impact of potentially beneficial and harmful effects on outcome, a forest plot of a random effects model is shown in Supplementary Table 26. Pooling all pertinent dichotomous variables by established directionality confirms no difference between the treatment groups' baseline characteristics with regard to their aggregate proposed effect on the primary outcome (OR 0.98, 95% CI: 0.69 – 1.39, P=0.91).

Discussion

We report the first-in-patient testing of FDY-5301, a novel pharmaceutical with potential to reduce acute ischemia-reperfusion injury in STEMI patients undergoing PPCI. We demonstrate, first, that FDY-5301 administration is feasible in the emergency setting of PPCI leading to a 1000-fold increase in plasma iodide concentration within two minutes of administration and prior to reopening of the infarct-related coronary artery. Second, that administration of FDY-5301 is safe with no clinically significant acute or long-term adverse effects. Third, that although not powered as a clinical efficacy study, the trends in CMR measures and biomarkers are favorable and support further evaluation in a large randomized study.

To be effective in the prevention of myocardial ischemia-reperfusion injury, any putative therapeutic must be formulated for rapid administration (so as not to delay PPCI) and must rapidly achieve therapeutic plasma levels in order to ensure bioavailability at or before the time of reperfusion. The importance of this was demonstrated as, although administration of drug was permitted by the protocol between 60 and 5 minutes prior to reperfusion, the median time of administration in this PPCI context was just 10 minutes before reperfusion. Intravenous FDY-5301 achieved an increase in plasma iodide concentration in STEMI patients of approximately 1000-fold, within 2 minutes after administration, similar to that seen in preclinical and Phase 1 human studies. This concentration of iodide (>10,000 parts per billion) exceeds the levels associated with anti-peroxidant biochemical effects and efficacy in pre-clinical models of acute MI.

A second pre-requisite for an effective therapeutic agent used in the context of STEMI is that any on-target beneficial effects on ischemia-reperfusion injury are not delivered at the expense of increased off-target harm, with arrhythmic risk as a primary safety concern. Reassuringly, FDY-5301 was well-tolerated by patients with STEMI undergoing PPCI, at doses up to 2 mg/kg, delivered as a single intravenous bolus. There were no acute adverse events that prevented or limited drug administration. There was no excess of serious adverse events in the period after PPCI, nor any serious or sustained ventricular arrhythmias. The only arrhythmias observed were transient non-sustained ventricular

tachycardias, predominantly in the first 24 hours, in some patients who received 2 mg/kg FDY-5301, and two cases of self-limiting heart block. This STEMI study is the first to use the evaluation of arrhythmias collected by continuous 14-day ambulatory ECG monitoring as a safety outcome in a clinical trial.

This phase 2a study was not powered to address the efficacy of FDY-5301 in reducing myocardial injury and final infarct size after acute STEMI. As expected, the range of infarct sizes quantified by cardiac MRI, and other biomarkers of myocardial injury such as troponin levels, were wide. This reflects the usual heterogeneity of patients presenting with acute MI, due to different infarct-related culprit vessels, different times to presentation, and a wide range of co-morbidities. Much larger patient groups would be required to detect a clinically meaningful change with adequate statistical power. Nevertheless, the trends observed in cardiac MRI-derived indices of infarct size and LV function all followed the same direction of reduced infarct size and improved LV function with increasing dose of FDY-5301. Furthermore, levels of NT-proBNP,[17] that are elevated in patients with AMI and associated with pulmonary capillary wedge pressure and reduced left ventricular ejection fraction,[16] were significantly reduced in the FDY-5301 treated groups. In addition, we observed that MPO levels decreased after PPCI in patients receiving FDY-5301, but not in placebo-treated patients. MPO is released from neutrophils,[24] and is known to be elevated in AMI [10], is associated with oxidative stress and inflammation,[25] and is thought to play a role in ischemia by inducing plaque rupture.[26, 27] One of the primary mechanisms of action of FDY-5301 is the reduction of inflammation and neutrophil chemotaxis,[7] through catalytic destruction of peroxides.[6] Finally, treatment with FDY-5301 also significantly reduced MMP-2, a marker of cardiac remodeling that is activated by oxidative stress.[28-27]

These findings are in keeping with our previously reported demonstration that sodium iodide improves outcome in models of acute myocardial infarction in mice, rats and pigs.[5, 6] In these experiments we conducted dose response curves for mice and rats and found that a range of doses between 0.25 and 2 mg/kg diminished infarct size. Sodium iodide at 1 mg/kg reduced infarct size by

70%, 60% and 45% in mice, rats and pigs, respectively. Echocardiographic assessments also showed functional improvements as measured by left ventricular ejection fraction and fractional shortening.

Limitations

The data presented are from a phase 2a study of FDY-5301 that was not designed or powered to investigate the clinical efficacy of FDY-5301. These data are hypothesis-generating for a future phase 3 study but are not evidence to support a change in current clinical practice. Arrhythmia data from the study was used to characterize the number and incidence rate of serious arrhythmias that occur during a 14-day interval in this patient population but no formal hypothesis testing with regard to safety outcomes was conducted and the arrhythmia data was intended to be descriptive in nature only. There remains the potential that other confounding co-variates could have impacted on these preliminary findings. However, in an exploratory analysis, although there was a univariate difference in opiate use between 2 mg/kg FDY-5301 and placebo groups, taking all potentially beneficial and harmful co-variates in combination, there was no difference between the treatment groups' baseline characteristics with regard to their aggregate proposed effect on primary outcome.

Conclusions

We have demonstrated that FDY-5301 can be administered rapidly and safely in patients with STEMI presenting in the emergency setting for PPCI. Administration of FDY-5301 immediately prior to PPCI leads to a ~1,000-fold increase in plasma iodide levels, before re-opening of the infarct-related coronary artery. FDY-5301 is not associated with clinically significant treatment-related adverse events in STEMI but is associated with a trend towards reduced final infarct size. FDY-5301 is a convenient and promising therapy to reduce ischemia-reperfusion injury in acute STEMI patients,

when administered prior to reperfusion during PPCI, and justifies further testing in larger randomized clinical trials.

TABLE 1. SUMMARY OF PATIENT CHARACTERISTICS

Demographic		Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
Age (years)	Mean	62	61	60	63	61
	SD	12.2	11.8	10.6	8.3	10.3
	N	29	29	31	31	91
Sex n (%)	Male	19 (66%)	24 (83%)	20 (65%)	20 (65%)	64 (70%)
	Female	10 (35%)	5 (17%)	11 (36%)	11 (36%)	27 (30%)
Weight (kg)	Mean	82.2	81.6	81.8	81.5	81.6
	SD	15.16	14.70	13.45	15.75	14.50
Height (cm)	Mean	170	173	171	170	172
	SD	8.3	7.8	8.2	10.7	9.0
BMI (kg/m^2)	Mean	28.5	27.1	28.0	28.1	27.7
	SD	4.43	4.17	4.29	4.88	4.44
Race n (%)	White	27 (93%)	29 (100%)	27 (87%)	30 (97%)	86 (95%)
	Black or African American	---	---	1 (3%)	---	1 (1%)
	Asian	1 (3%)	---	1 (3%)	---	1 (1%)
	American Indian or Alaskan	---	---	1 (3%)	---	1 (1%)
	Other	1 (3%)	---	1 (3%)	1 (3%)	2 (2%)
Pain-to-balloon time (minutes)	Median	252	208	229.5	200	213.5
	Range (Q1-Q3)	142-372	174-353	133-343	148-350	160-350
Door-to-balloon time (minutes)	Median	34	34	42.5	40	36
	Range (Q1-Q3)	23-51.5	23-42	26-71	28-52	27-55

Hypertension	N (%)	15 (51.7%)	10 (34.5%)	9 (29.0%)	16 (51.6%)	35 (38.5%)
Diabetes Mellitus	N (%)	4 (13.8%)	1 (3.4%)	4 (12.9%)	4 (12.9%)	9 (9.9%)
Hyperchol.	N (%)	3 (10.3%)	1 (3.4%)	2 (6.5%)	4 (12.9%)	7 (7.7%)
Prior AMI	N (%)	---	---	2 (6.5%)	---	2 (2.2%)
Anterior STEMI	N (%)	9 (31.0%)	13 (44.8%)	9 (29.0%)	10 (32.3%)	32 (35.2%)
Pre medications[1] N (%)	ACE inhibitors	7 (24.1%)	5 (17.2%)	3 (9.7%)	6 (19.4%)	14 (15.3%)
	ARBs	1 (3.4%)	2 (6.9%)	1 (3.2%)	5 (16.1%)	8 (8.8%)
	Aspirin	7 (24.1%)	5 (17.2%)	12 (38.7%)	10 (32.3%)	27 (29.7%)
	Beta blockers	5 (17.2%)	2 (6.9%)	4 (12.9%)	7 (22.6%)	13 (14.3%)
	Insulin	1 (3.4%)	1 (3.4%)	---	2 (6.5%)	3 (3.3%)
	Opioids	1 (3.4%)	4 (13.8%)	5 (16.1%)	4 (12.9%)	13 (14.3%)
	P2Y12 inhibitors	6 (20.7%)	6 (20.7%)	11 (35.5%)	8 (25.8%)	25 (27.5%)
	Statins	6 (20.7%)	5 (17.2%)	5 (16.1%)	10 (32.3%)	20 (22.0%)
Peri-procedural medications[2] N (%)	ACE inhibitors	8 (27.6%)	3 (10.3%)	5 (16.1%)	6 (19.4%)	14 (15.4%)
	ARBs	1 (3.4%)	2 (6.9%)	1 (3.2%)	3 (9.7%)	6 (6.6%)
	Aspirin	11 (37.9%)	16 (55.2%)	16 (51.6%)	18 (58.1%)	50 (54.9%)
	Beta blockers	8 (27.6%)	4 (13.8%)	6 (19.4%)	6 (19.4%)	16 (17.6%)
	Insulin	1 (3.4%)	1 (3.4%)	---	2 (6.5%)	3 (3.3%)
	Opioids	14 (48.3%)	15 (51.7%)	10 (32.3%)	12 (38.7%)	37 (40.7%)
	P2Y12 inhibitors	17 (58.6%)	14 (48.3%)	16 (51.6%)	16 (51.6%)	46 (50.5%)
	Statins	10 (34.5%)	7 (24.1%)	9 (29%)	12 (38.7%)	28 (30.8%)
Post-procedural medications[3] N (%)	ACE inhibitors	20 (69%)	24 (82.8%)	24 (77.4%)	21 (67.7%)	69 (75.8%)
	ARBs	5 (17.2%)	1 (3.4%)	3 (9.7%)	4 (12.9%)	8 (8.8%)
	Aspirin	24 (82.8%)	27 (93.1%)	26 (83.9%)	27 (87.1%)	80 (88.0%)
	Beta blockers	20 (69%)	26 (89.7%)	29 (93.5%)	24 (77.4%)	79 (86.8%)
	Insulin	1 (3.4%)	---	1 (3.2%)	2 (6.5%)	3 (3.3%)
	Opioids	1 (3.4%)	6 (20.7%)	5 (16.1%)	---	11 (12.1%)
	P2Y12 inhibitors	22 (75.9%)	28 (96.6%)	25 (80.6%)	26 (83.9%)	79 (86.8%)

Demographic	Placebo	0.5 mg/kg FDY-5301	1.0 mg/kg FDY-5301	2.0 mg/kg FDY-5301	All FDY-5301
Statins	23 (79.3%)	27 (93.1%)	28 (90.3%)	27 (87.1%)	82 (90.1%)

[1]Medications taken prior to symptoms/study
[2]Medications taken after symptoms and no more than 2 hours after PCI start
[3]Medications taken more than 2 hours after PCI start

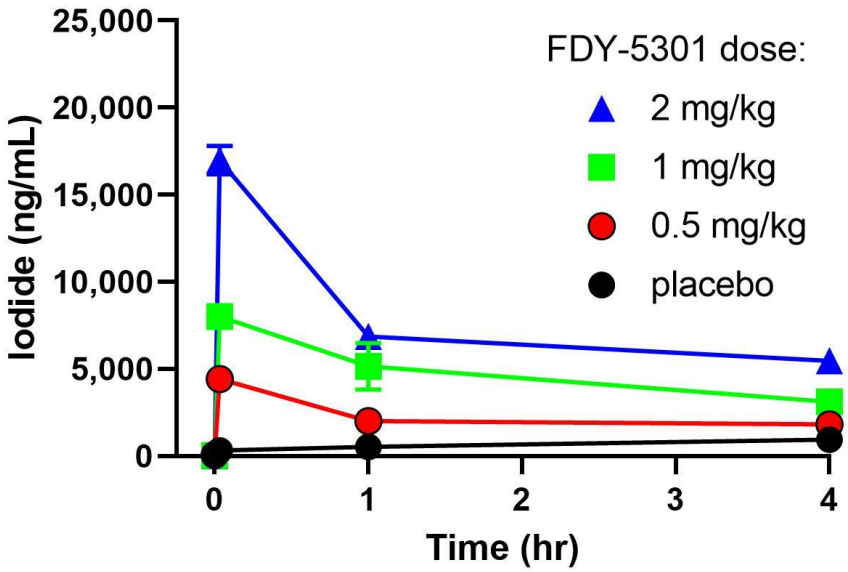

Figure 1. Plasma Pharmacokinetics of FDY-5301

The levels of iodide were assayed in plasma at baseline and at either 2 minutes, 1 hour or 4 hours after administration of either placebo or FDY-5301. Points show mean ± SEM.

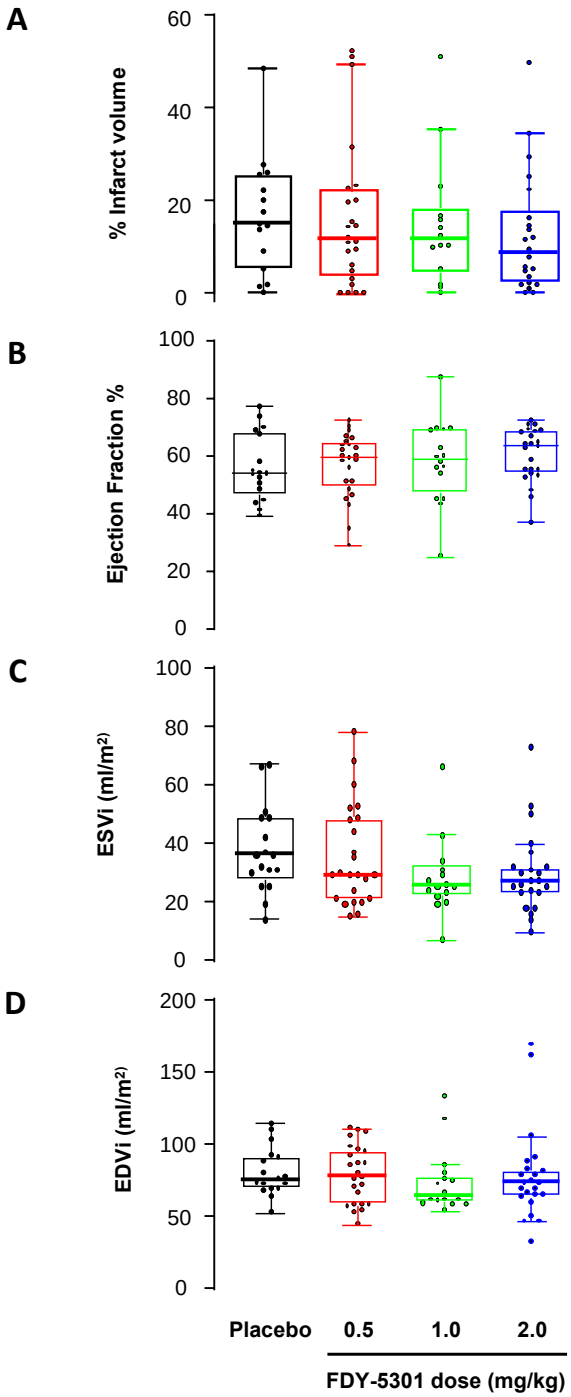

Figure 2 – Effects of FDY-5301 on Final Infarct Size after STEMI

Cardiac MRI at three months was used to quantify final infarct size (by late gadolinium enhancement, expressed as percentage of total LV volume; Panel A), LV ejection fraction (Panel B), end systolic volume index (ESVi, Panel C) and end diastolic volume index (EDVi, Panel D). Boxes show 25th centile- 75th centile with median, whiskers show 10th-90th centiles.

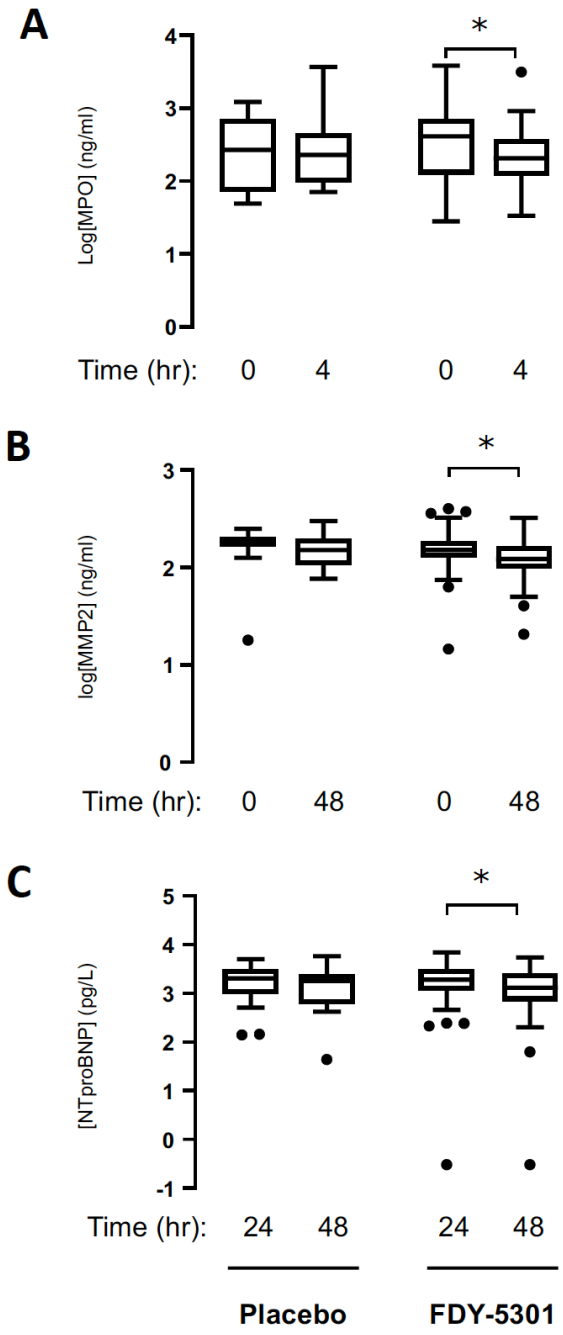

Figure 3 – Plasma Biomarkers of Inflammation, LV Dysfunction and LV Remodeling After administration of FDY-5301

The levels of myeloperoxidase (MPO, Panel A), matrix metalloproteinase 2 (MMP-2, Panel B) and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP, Panel C) were assayed in plasma at baseline and at either 4 hours (for MPO) or 48 hours (for MMP-2 and NT-proBNP) after administration of either placebo or FDY-5301. Data are plotted at the Log of concentrations. Boxes show 25th centile- 75th centile with median, whiskers show 10th-90th centiles.

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