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

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Faraday PHARMACEUTICALS

British Heart Foundation

FDY-5301 Mechanism of Action

- FDY-5301 delivered by intravenous bolus injection rapidly **increases blood iodide** levels, has undergone extensive preclinical and phase 1 human testing in healthy volunteers

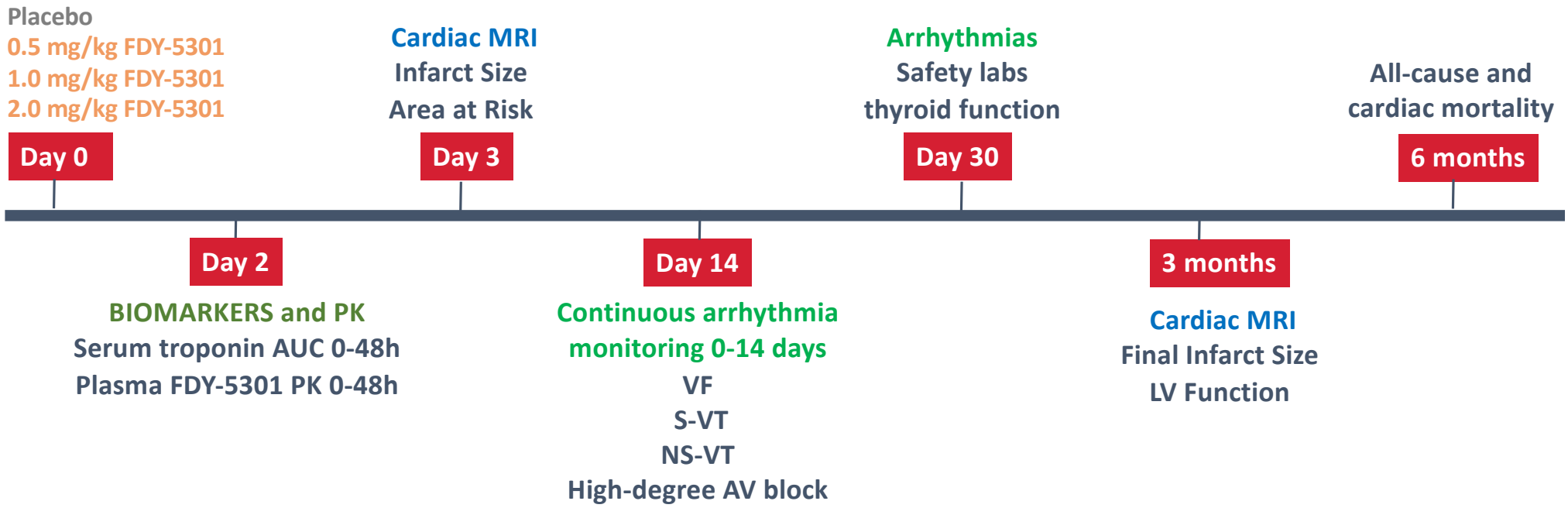
- Iodides (I^-) are elemental reducing agents (ERAs) that can **break down reactive oxygen species (ROS)** at supra-physiological concentration; oxidized iodine anions (e.g. iodate IO_3^-) have no effect

- ROS such as H_2O_2 are produced very rapidly after reperfusion in STEMI, mediating ischemia-reperfusion injury, induction of apoptosis, inflammatory responses and immune modulation

- FDY-5301 reduces myocardial damage and inflammation in pre-clinical models of ischemia/reperfusion in mice, pigs and rats (Iwata, Morrison & Roth, *PLoS ONE* 2015)

STUDY DESIGN – Randomized, Double Blind, Dose Ranging Phase 2a

First STEMI
0-12H pain-to-balloon time
PPCI + single I.V. dose prior to reperfusion:



STUDY DEMOGRAPHICS

Mean Age (years)	62
Mean Weight (kg)	82
Male Patients (%)	70
Type 1 Diabetes Mellitus	1
Type2 Diabetes Mellitus	9 (4 in 2mg/kg group)
Patients with previous MI	2 (both in 1 mg/kg)
LAD Culprit Vessel (%)	34.2
Initial TIMI Flow 0/1 (%)	78.3
Pain-to-Balloon Time (Median)	220 mins

N=120 Randomized
N=12 Withdrew
N=3 Died

Continuous ECG monitoring via wearable sensors 14 days of monitoring starting immediately post-PPCI

-Ventricular Fibrillation
-Sustained VT ≥ 125 BPM, ≥ 30 Seconds
-Non-sustained VT ≥ 125 BPM, < 30 Seconds
-2nd or 3rd Degree AV block ≥ 8 Beats

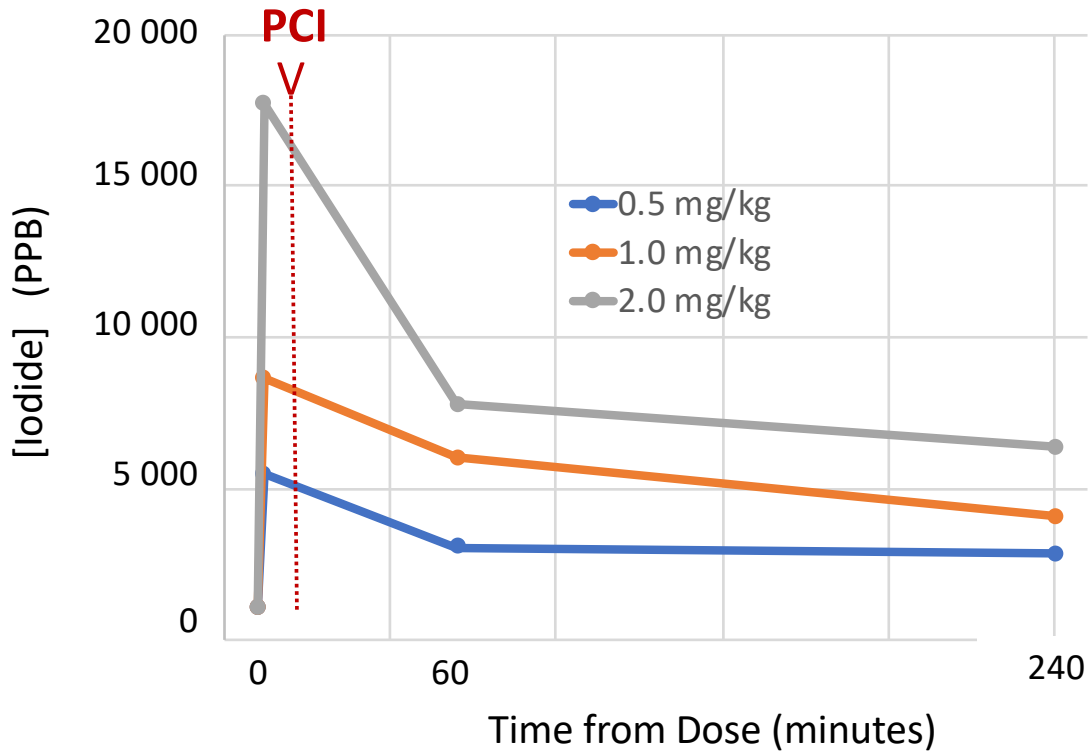
Primary Outcome
Post-STEMI arrhythmias (0-14 Days)

Secondary Outcomes

MRI Infarct size relative to LV at 3 days and 3 months
Cardiac function (LVEF, ESVi and EDVi) at 3 months
Serum troponin AUC 0-48h
Adverse events
Safety labs including thyroid hormones
Plasma sodium iodide concentrations 0-48h

FDY-5301 - Pharmacokinetics

Median Time from Dose Administration to PCI : **10** (6-19) minutes – **1000 fold increase in [iodide]**



Arrhythmias in the First 14 days Post-Treatment

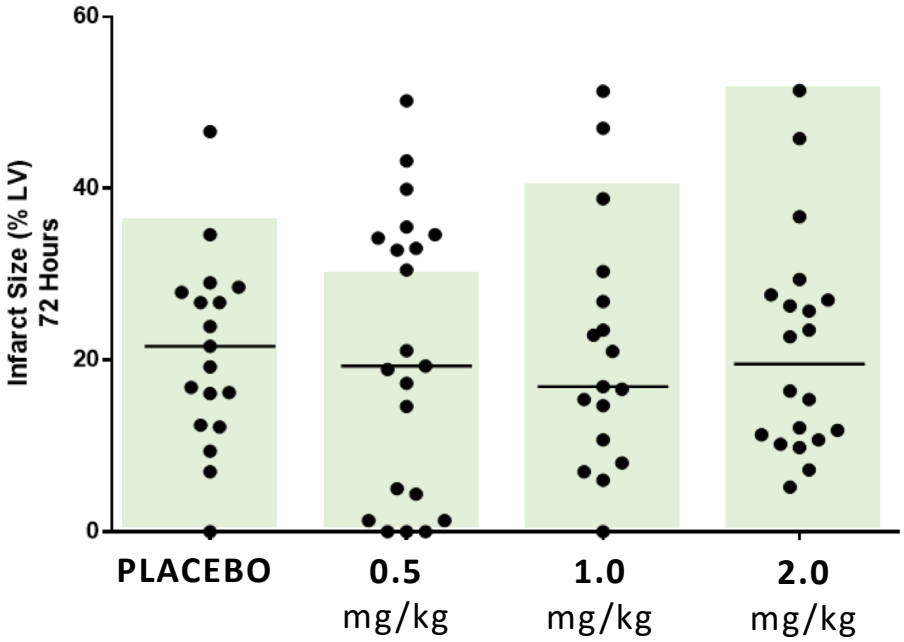
N=113

No incidents of VF or sustained VT occurred in any treatment group during monitoring

Non-sustained VT and AF occurred in patients from all treatment groups primarily in the first 48 hours. There was a slight excess of non-sustained VT in the 2 mg/kg FDY-5301 group which resolved within 48 hours.

Two patients in the 2 mg/kg FDY-5301 treatment group experienced self-limiting 2nd degree AV block without clinical or hemodynamic consequence.

Myocardial Injury at 72 Hours by CMR (% LV)



Green = Median LV Area at Risk

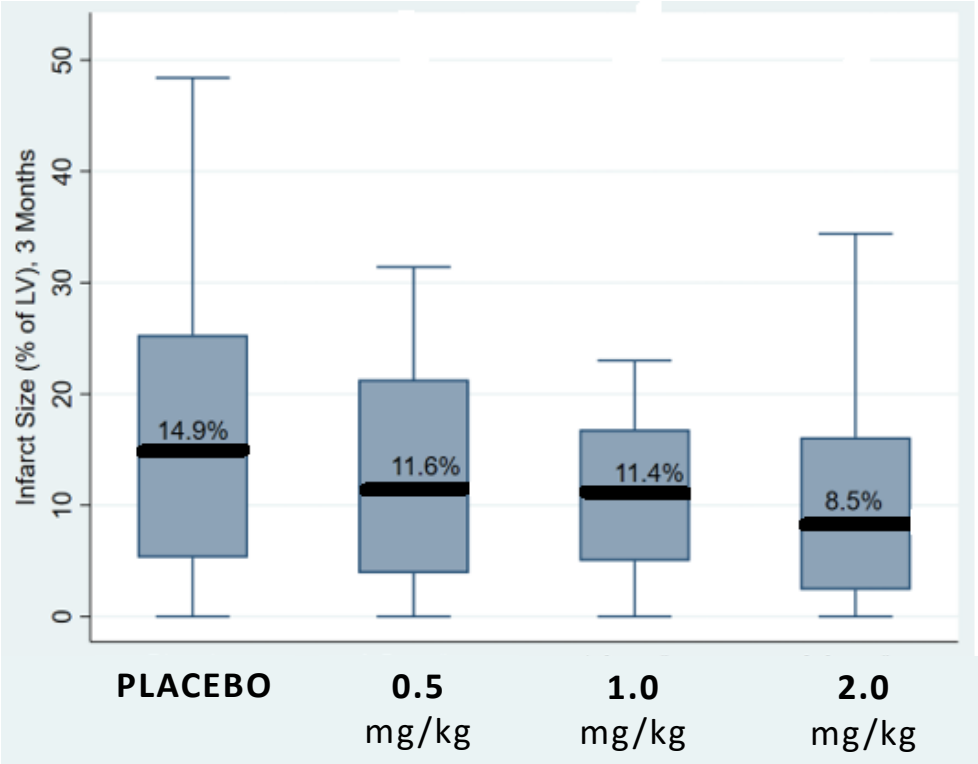
Placebo= 35.3%

0.5 mg/kg FDY-5301=30.5%

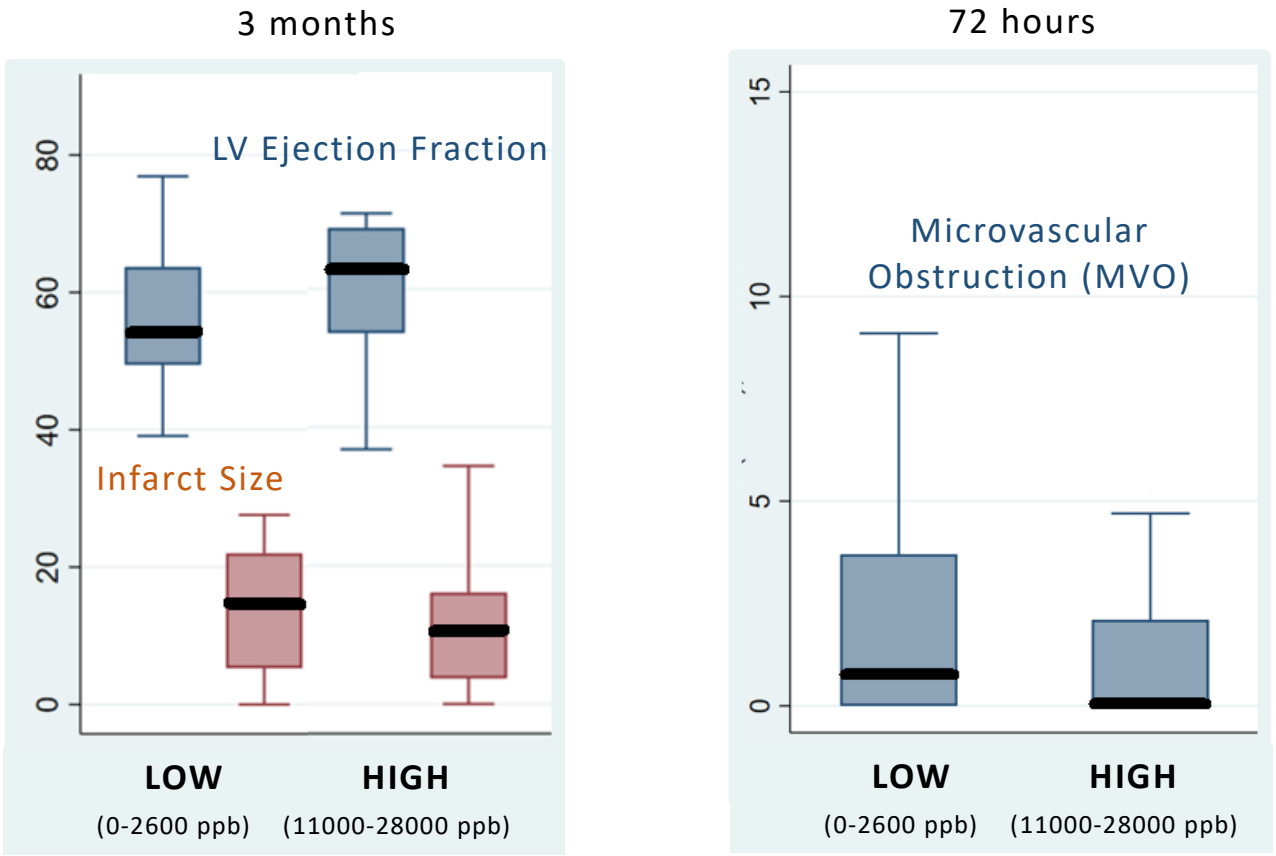
1.0 mg/kg FDY-5301=39.7%

2.0 mg/kg FDY-5301=50.7%

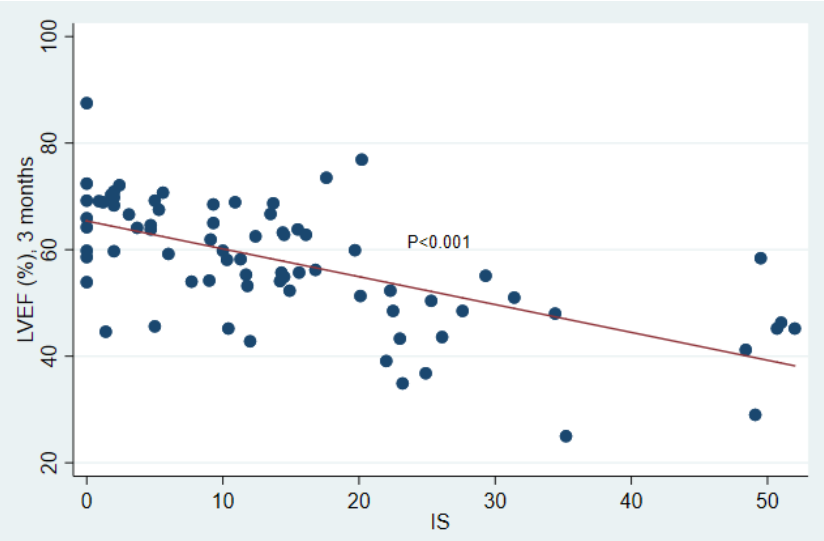
Infarct Size at 3 months by CMR (% LV)

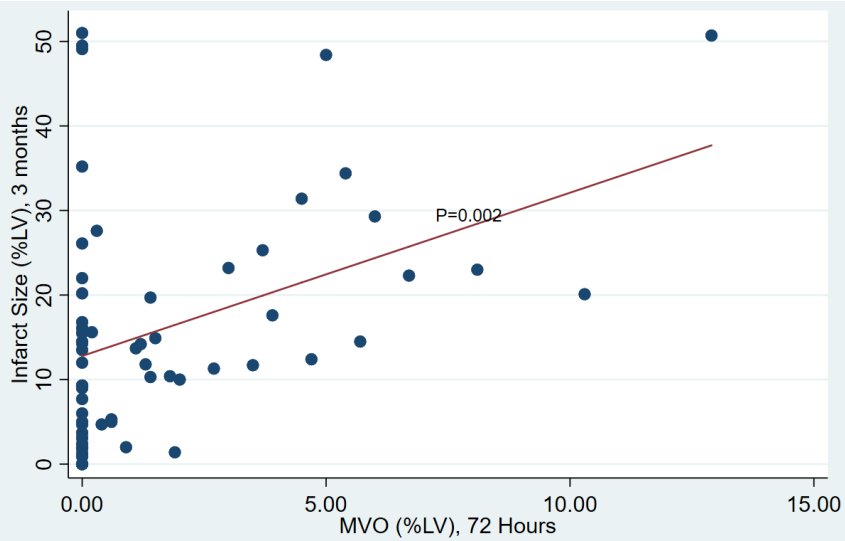


Infarct Size and LVEF by Plasma [Iodide] C_{max} Quartiles



Infarct Size vs. LVEF, Infarct Size vs. MVO





FDY-5301 dose (mg/kg)

Treatment Group	R^2	P value
0	.15	.15
0.5	.56	<0.001
1.0	.54	.003
2.0	.29	.01

Conclusions

FDY-5301 is a safe and easy to administer in the emergency setting of acute STEMI

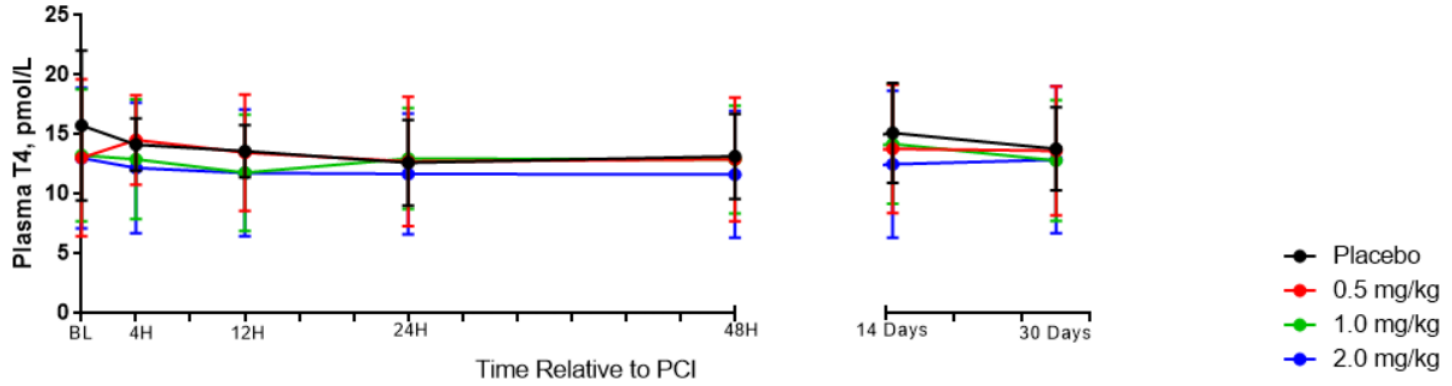
FDY-5301 increases blood iodide levels by 1000-fold within 2 minutes, *before* opening of the coronary artery in STEMI

In STEMI patients, FDY-5301 had no significant adverse outcomes and showed promising efficacy trends in infarct size and LV function

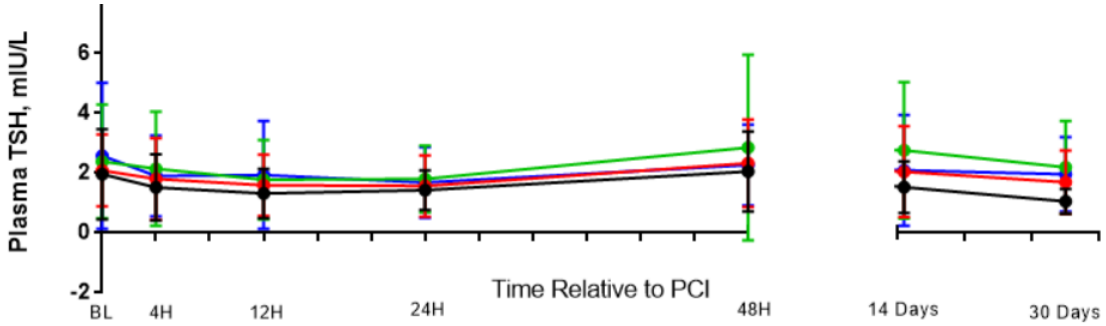
These safety and feasibility data strongly support a larger clinical trial to test the benefit of FDY-5301 to improve outcomes after STEMI

Effects on Thyroid Function

T4

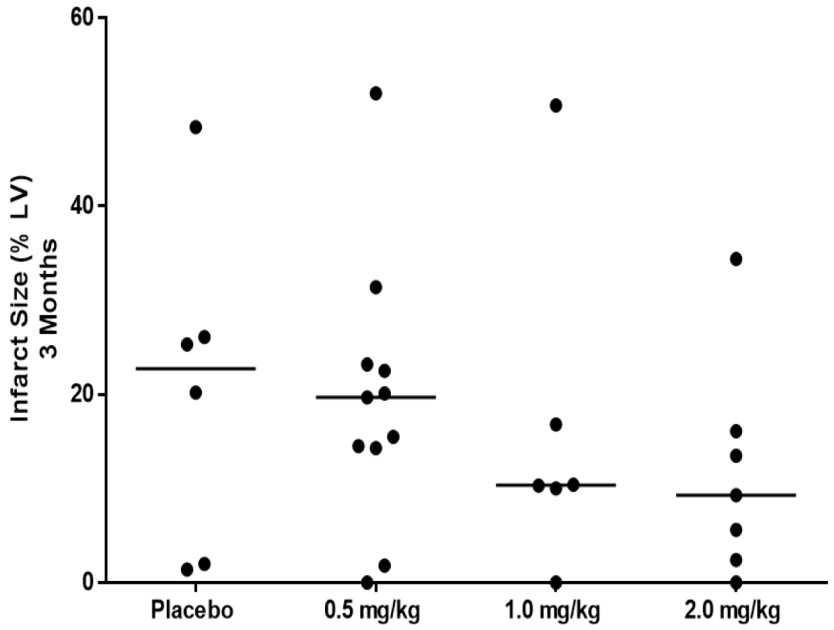


TSH

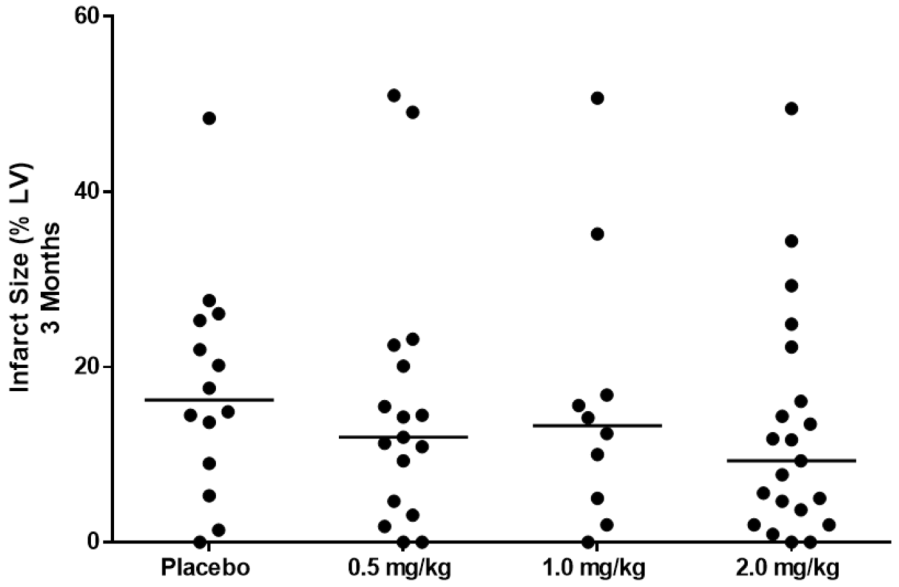


Infarct Size 3 Months Stratified Analysis

Patients With Anterior STEMI



Patients With TIMI 0-1



FDY-5301 safety data

	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)
Patients with AE's	20 (69.0%)	17 (58.6%)	14 (45.2%)	13 (49.1%)
Number of AE's	54	41	31	18
Patients with SAE's	8 (27.6%) [10]	7 (24.1%) [12]	7 (22.6%) [12]	4 (12.9%) [5]
Patients Discontinued due to death	1 (3.4%)	---	1 (3.2%)	1 (3.2%)
Patients with Cardiac related AE's	3 (10.3%) [5]	8 (27.6%) [11]	8 (25.8%) [12]	8 (25.8%) [8]
Patients with Cardiac related SAE's	3 (10.3%) [4]	5 (17.2%) [6]	7 (22.6%) [10]	3 (9.7%) [3]

AE	Placebo	.5	1.0	2.0
Atrial Fibrillation		2 (1*)		
Anterior STEMI (related to Stent Thrombosis)		1*		
Cardiac Sounding Chest Pain (episode)				1
Cardiogenic Shock	1*		1**	1
Chest Pain/Angina Pectoris			3	1
Congestive & Acute Congestive heart failure episode with low cardiac output			1**	
Coronary Artery Disease			1	
Coronary Artery Perforation			1*	
Heart failure	1			
Left Ventricular Thrombus		1		
LMCA/LAD Dissection		1		
Multivessel Coronary Artery disease		1		
Papillary Muscle rupture requiring repair	1*			
Percutaneous Coronary Intervention				1
Stent Thrombosis	1	1*		
Ventricular Fibrillation	1			
Ventricular Fibrillation Arrest			1*	
	*Same patient	*Same patient	*Same patient ** Same patient	