The SELECT-ACS Trial

Effects of the P-selectin antagonist inclacumab on myocardial damage after PCI for NSTEMI

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on behalf of the SELECT-ACS steering committee

Background

- Myocardial damage is common after PCI, due in part to inflammation and platelet activation.
- P-selectin, a cell adhesion molecule expressed on activated endothelial cells and platelets, plays a critical role in leukocyte and platelet rolling.
- Animal studies have suggested that inhibition of P-selectin decreases neutrophil and platelet adhesion, macrophage accumulation and neointimal formation after injury.

Inclacumab

- Fully human recombinant monoclonal IgG4 antibody
- Mutated Fc portion, elimination of effector functions by IgG4 conversion and L235E mutation
- High selectivity (3000 fold) for P-selectin vs E- and L-selectin
- No adverse findings in non-clinical safety profiling
- Anti-inflammatory + antithrombotic effects: in vitro assays, ex vivo human flow system, in vivo inflammation model
- Reduction in CD11b expression on neutrophils

Study objective

To determine the efficacy of inclacumab in reducing myocardial damage during percutaneous coronary intervention (PCI) in patients with non-ST elevation MI (NSTEMI)

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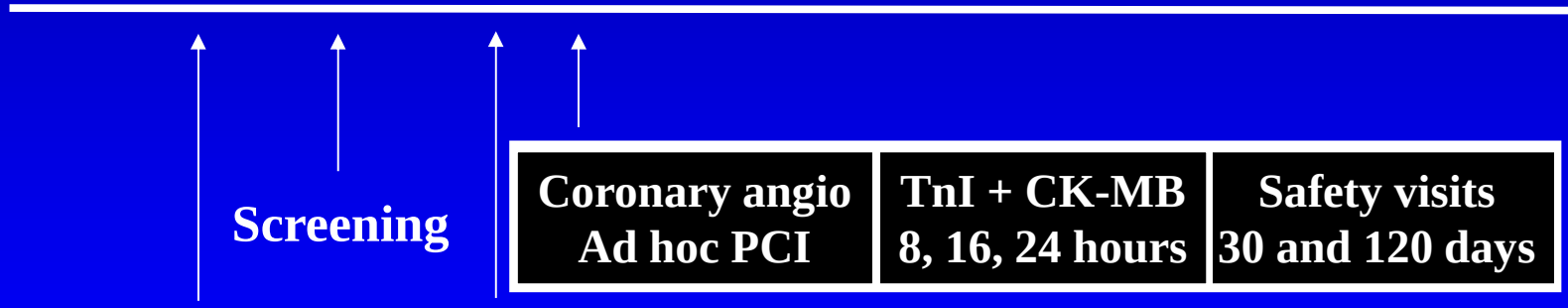
Study design

- 18-85 years
- NSTEMI
- TnI or CK-MB above 99th percentile
- Scheduled for cath and ad hoc PCI

Randomization

- Placebo (1 infusion)
- Inclacumab 5 mg/kg (1 infusion)
- Inclacumab 20 mg/kg (1 infusion)



NSTEMI Study drug infusion
1-24 hrs pre-PCI

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Exclusion criteria

- PCI within past 72 hours, recent thrombolysis
- Recent cerebral vascular disease or stroke
- Bleeding disorders, blood dyscrasia
- Severe uncontrolled hypertension
- Prior CABG surgery
- Active or chronic infection
- Severe inflammatory or auto-immune disease
- Uncontrolled diabetes
- Hepatic failure, severe renal failure

Efficacy and safety endpoints

Primary efficacy endpoint

- Change in troponin I at 16 and 24 hours post-PCI

Secondary efficacy endpoints

- Peak troponin I (TnI) post-PCI
- Area under the curve for TnI over 24 hours
- Change in TnI at 8 hours post-PCI
- Changes in CK-MB at 8, 16 and 24 hrs post-PCI

Safety analysis (in all patients who received infusion)

- AEs, lab results, physical exam, vital signs, ECG

Patient flow

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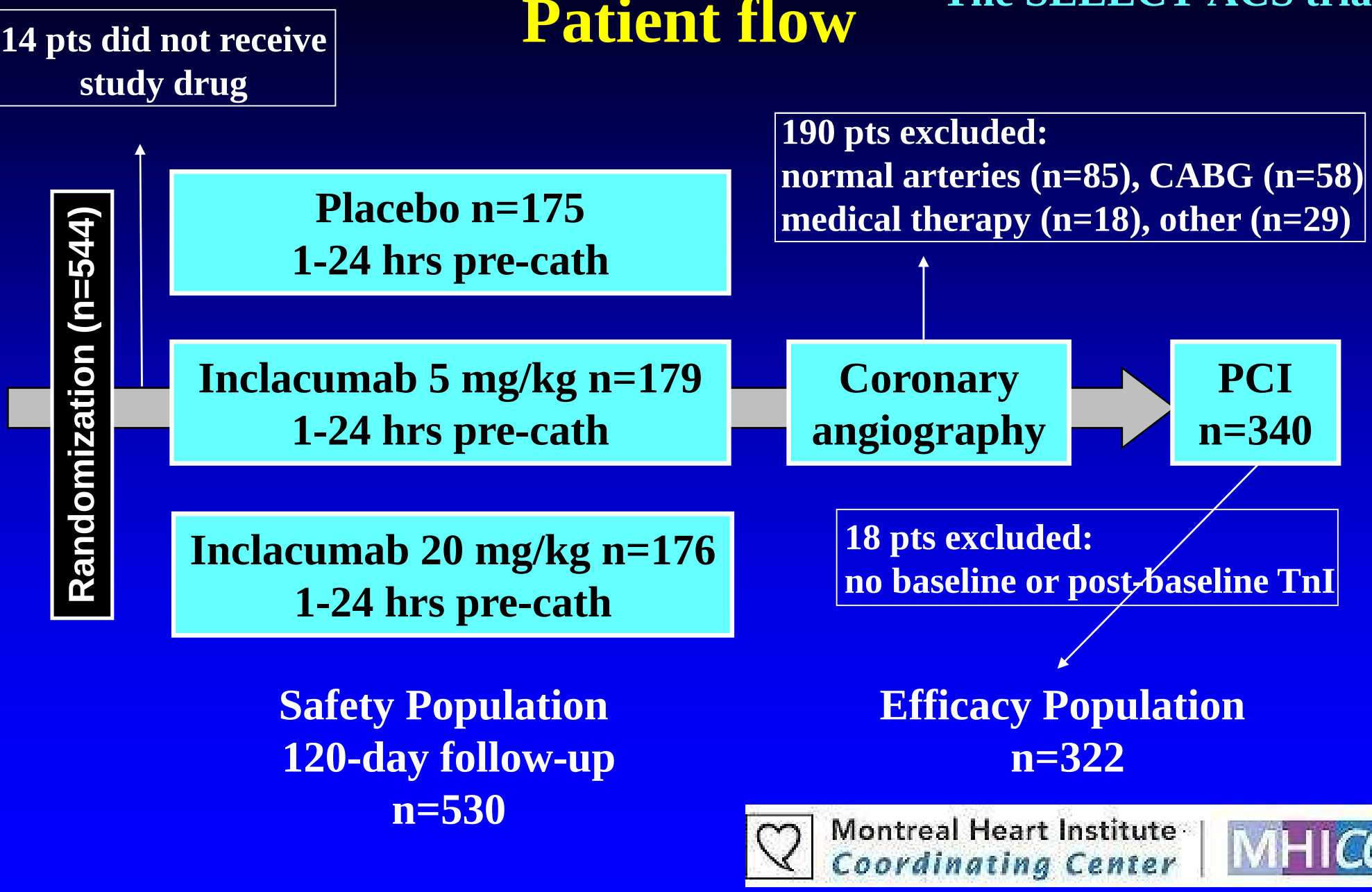

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Baseline characteristics

	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)
Age (yrs, median)	60.9	63.1	59.8
Men (%)	79.1	77.9	79.5
Caucasians (%)	95.7	95.8	96.4
Diabetes (%)	20.9	24.2	23.2
Duration of PCI (min)	20.0	22.0	25.5
Ref. vess. diameter (mm)	3.0	3.0	3.0
Total stent length (mm)	22.0	20.0	22.0
Drug-eluting stent (%)	59.2	58.6	56.5
Bare metal stent (%)	35.4	35.3	39.1

Concomitant medications

	Placebo (n = 115)	Inclacumab 5 mg/kg (n = 95)	Inclacumab 20 mg/kg (n = 112)
P2Y12 inh. pre-PCI (%)	79.8	78.5	81.8
Gp 2b3a antagonists (%)	17.4	16.8	19.6
Aspirin (%)	96.6	91.1	92.0
Statins (%)	96.0	94.4	94.9
ACE inhibitors (%)	75.4	71.5	79.0
ARBs (%)	14.3	19.0	9.7
Beta-blockers (%)	90.3	90.5	92.0

Change in troponin I at 24 hours

Troponin I (TnI)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean I.Q.R.	1.03 0.24-4.69	0.71 0.17-3.44	0.82 0.19-3.73
24 hours post-PCI	1.76	1.21	0.99
Change from baseline[1]	57.7%	55.5%	19.1%
Placebo-adjusted change[2] 95% C.I. p-value	-- --	-1.4% (-26.7, 32.7) 0.93	-24.4% (-43.1, 0.4) 0.05

[1]Adjusted geometric mean %change (based on repeated ANCOVA model).
[2]Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

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Change in troponin I at 16 hours

Troponin I (TnI)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean I.Q.R.	1.03 0.24-4.69	0.71 0.17-3.44	0.82 0.19-3.73
16 hours post-PCI	1.74	1.30	1.09
Change from baseline[1]	77.4%	71.3%	37.6
Placebo-adjusted change[2] 95% C.I. p-value	-- --	-3.4% (-27.2, 28.2) 0.81	-22.4% (-40.8, 1.7) 0.07

[1]Adjusted geometric mean %change (based on repeated ANCOVA model).
[2]Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

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Change in peak troponin I and AUC

Troponin I (TnI)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Peak TnI geometric mean	2.09	1.56	1.34
Placebo-adjusted change[1] 95% C.I. p-value	--	-1.5% (-26.3, 31.6) 0.92	-23.8% (-42.2, 0.5) 0.05
Area under the curve	40.37	28.87	26.35
Placebo-adjusted change 95% C.I. p-value	-- --	-27.2% (-54.8, 17.2) 0.19	-33.9% (-58.1, 4.3) 0.08

[1]Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

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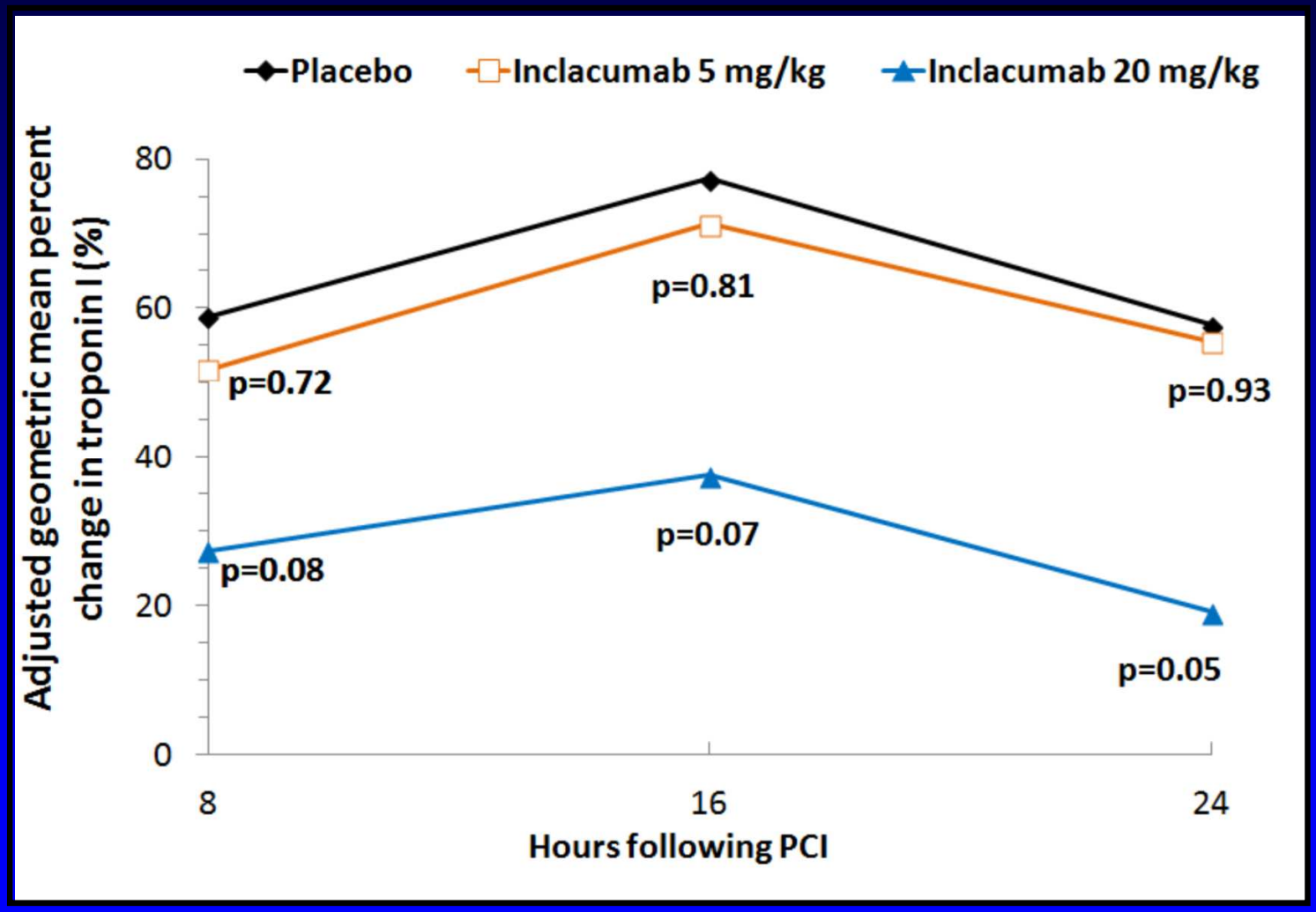
Percent change in troponin I over time



Change at 24 hrs with inclacumab 20 mg/kg vs pbo: diabetics -33.2%, non-diabetics -31.6% (p=0.03)

Change in CK-MB at 24 hours

CK-MB	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean I.Q.R.	9.46 3.60-23.70	7.54 2.70-15.50	7.97 3.10-17.85
24 hours post-PCI	8.07	6.57	5.83
Change from baseline[1]	-15.0%	-19.0%	-29.8
Placebo-adjusted change[2] 95% C.I. p-value	-- --	-4.7% (-22.3, 16.9) 0.64	-17.4% (-32.1, 0.4) 0.06

[1] Adjusted geometric mean %change (based on repeated ANCOVA model).
[2] Placebo-adjusted geometric mean %change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

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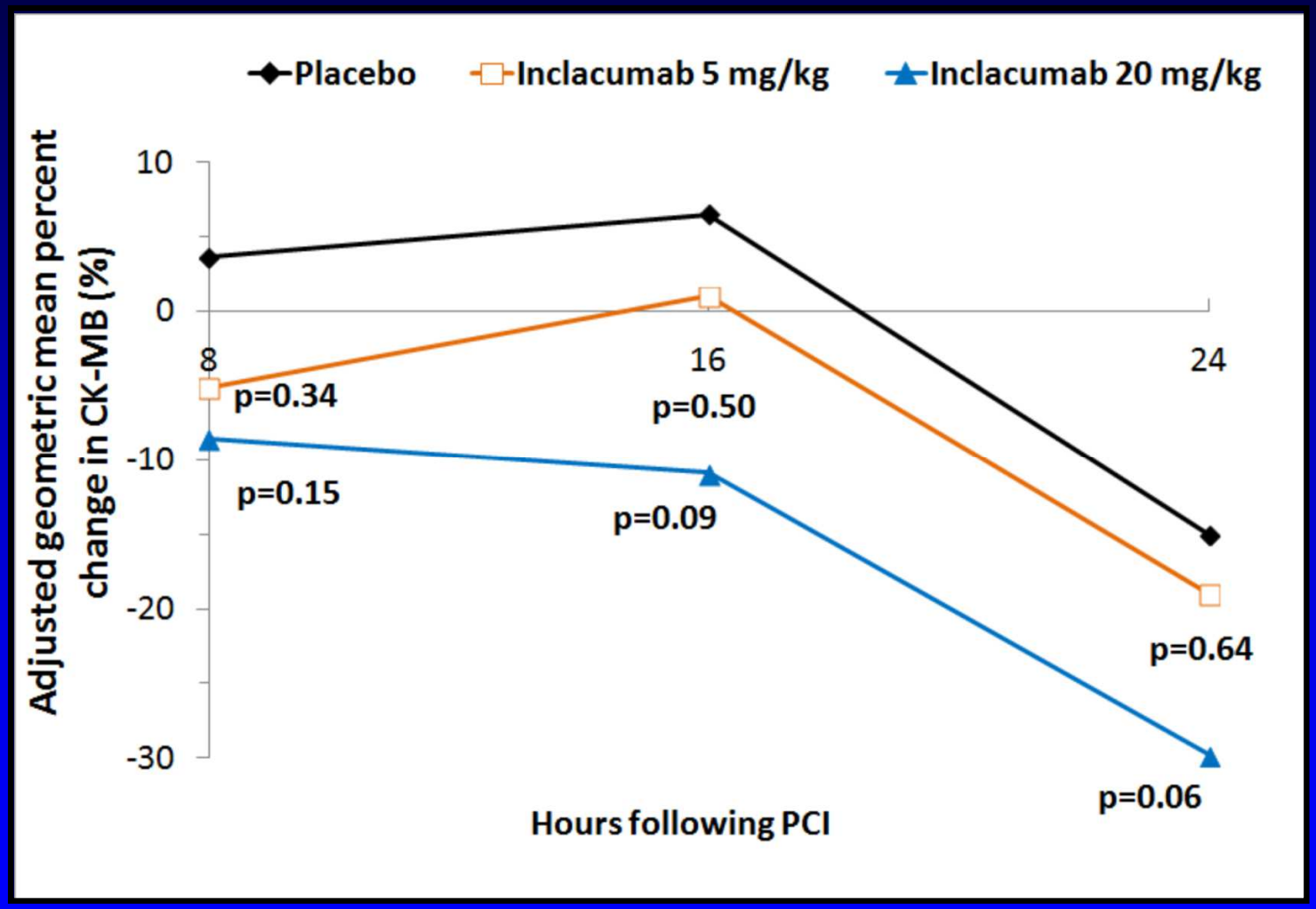
Percent change in CK-MB over time



Incidence of CK-MB increases >3 X ULN:
placebo 18.3%, inclacumab 20 mg/kg 8.9% (p=0.05)

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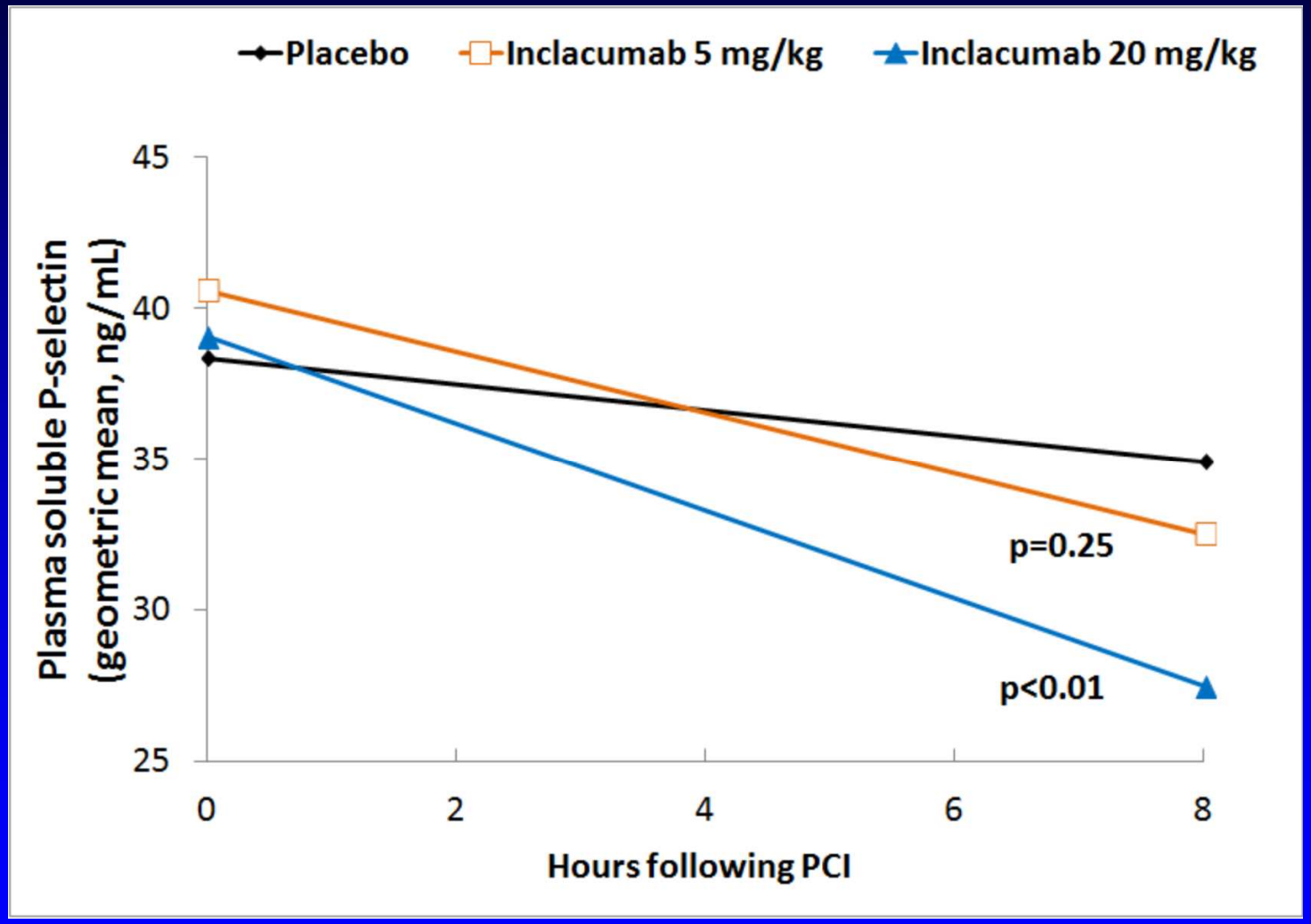
Plasma soluble P-selectin level after PCI



Placebo-adjusted GM percent change:
-22.0% with inclacumab 20 mg/kg (p<0.01)

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Safety summary

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	Placebo (n = 175)		Inclacumab 5 mg/kg (n = 179)		Inclacumab 20 mg/kg (n = 176)	
	n	%	n	%	n	%
Serious adverse events	32	18.3	43	24.0	45	25.6
Adverse events	106	60.6	111	62.0	112	63.6
Infection	21	12.0	19	10.6	19	10.8
Bleeding up to 120 days	9	5.1	11	6.1	7	4.0
All-cause death	0		4		2	
*Non-fatal MI	2		4		7	
Stroke	0		0		1	
Hospitalization for ACS	2		1		1	
Resuscitated cardiac arrest	1		2		1	
Revascularization procedures	20		31		22	

**Some peri-PCI MIs were reported as non-fatal MIs according to investigator's judgement*

Limitations

- Efficacy analyses were conducted in patients who received the infusion, underwent PCI and had TnI levels available at baseline and follow-up.
- Several results were of borderline statistical significance.
- Study not powered for evaluation of clinical endpoints.
- While TnI and CK-MB are reliable biomarkers of myocardial damage, the clinical significance of post-PCI elevations remains open to debate.

Conclusions

- The consistency of our data suggests that the P-selectin antagonist inclacumab reduces myocardial damage after PCI in patients with NSTEMI.
- Further clinical investigation will be required to determine the clinical value (benefit or harm) of inclacumab in patients presenting with myocardial infarction whether or not they undergo PCI.