

A proof of concept study of the effect of ADX10059, an mGluR5 NAM, on acid exposure and symptoms in gastro-oesophageal reflux disease.

Introduction and Rationale

- ADX10059 is a negative allosteric modulator (NAM) of metabotropic glutamate receptor 5 (mGluR5)
- Allosteric modulators act on receptor binding sites distant from that of natural ligand to enhance (PAM) or reduce (NAM) activity of the natural ligand.
- Non competitive with natural ligand – “dimmer switch”
- Synthetic small molecule, oral administration.
- Data from models of GERD in dogs and ferrets showed that related mGluR5 NAM compounds MPEP and MTEP reduced TLESRs and increased LES tone.
- This was the first experiment of an mGluR5 NAM in patients with GERD.

Study design



- ◆ Single-blind (patient), placebo-controlled trial of the effect of two doses of ADX10059 on 24 hour esophageal pH in patients with GERD
- ◆ Two sequential single day treatments, t.i.d administration 30min before a standard meal
- ◆ 24 hour oesophageal pH monitoring and symptom reporting on each day
- ◆ Day 1 placebo, Day 2 ADX10059
- ◆ Dose Group 1: ADX10059 50mg t.i.d, Group 2: ADX10059 250mg t.i.d.
- ◆ Male and female patients with GERD not on acid suppressant therapy
- ◆ Primary objective: Effect of treatment on 24 hour oesophageal pH
- ◆ Secondary objectives: Effect of treatment on post-prandial reflux and symptoms or reflux, safety, tolerability and pharmacokinetics

Patient characteristics

Characteristic	ADX10059 50 mg N = 12	ADX10059 250 mg N = 12
Race (Caucasian)	12 (100%)	12 (100%)
Sex (female)	3 (25%)	2 (16.7%)
Age (years)	44.6	45.1
Weight (kg)	77.9	79.8
BMI (kg/m²)	26.1	26.2
Light smokers (<5 cigarettes per day)	3 (25.0%)	2 (16.7%)
Previous GERD medications	6 (50%)	10 (83.3%)

Primary Efficacy: 24 hour pH



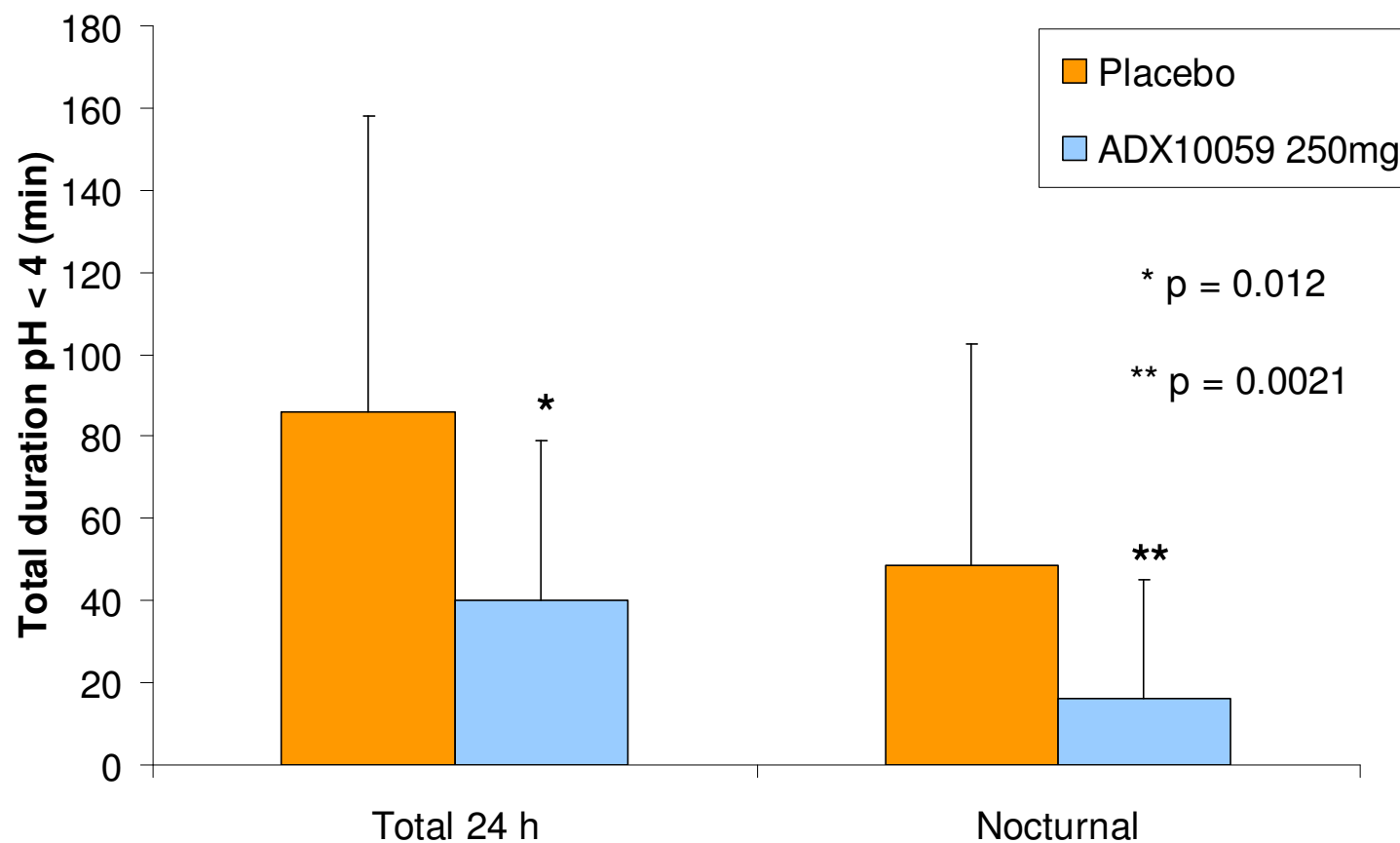
Treatment Group	% time pH < 4 in 24h	% time pH < 4 diurnal	% time pH < 4 nocturnal
Group 1 n = 12			
Placebo	14.9	9.5	22.7
ADX10059 50 mg	15.1	12.8	18.9
Estimate change from baseline	2.71	4.75	0.19
95% CI	[-2.05; 7.48]	[0.14;9.37]	[-5.88; 6.26]
P value	ns	0.0442*	ns
Group 2 n = 11			
Placebo	7.2	5.2	9.7
ADX10059 250 mg	3.6	3.4	3.7
Estimate change from baseline	-6.41	-3.41	-10.37
95% CI	[-11.4; -1.42]	[-8.24; 1.42]	[-16.73; -4.01]
P value	0.0144	ns	0.0028

Efficacy summary ADX10059 250 mg t.i.d

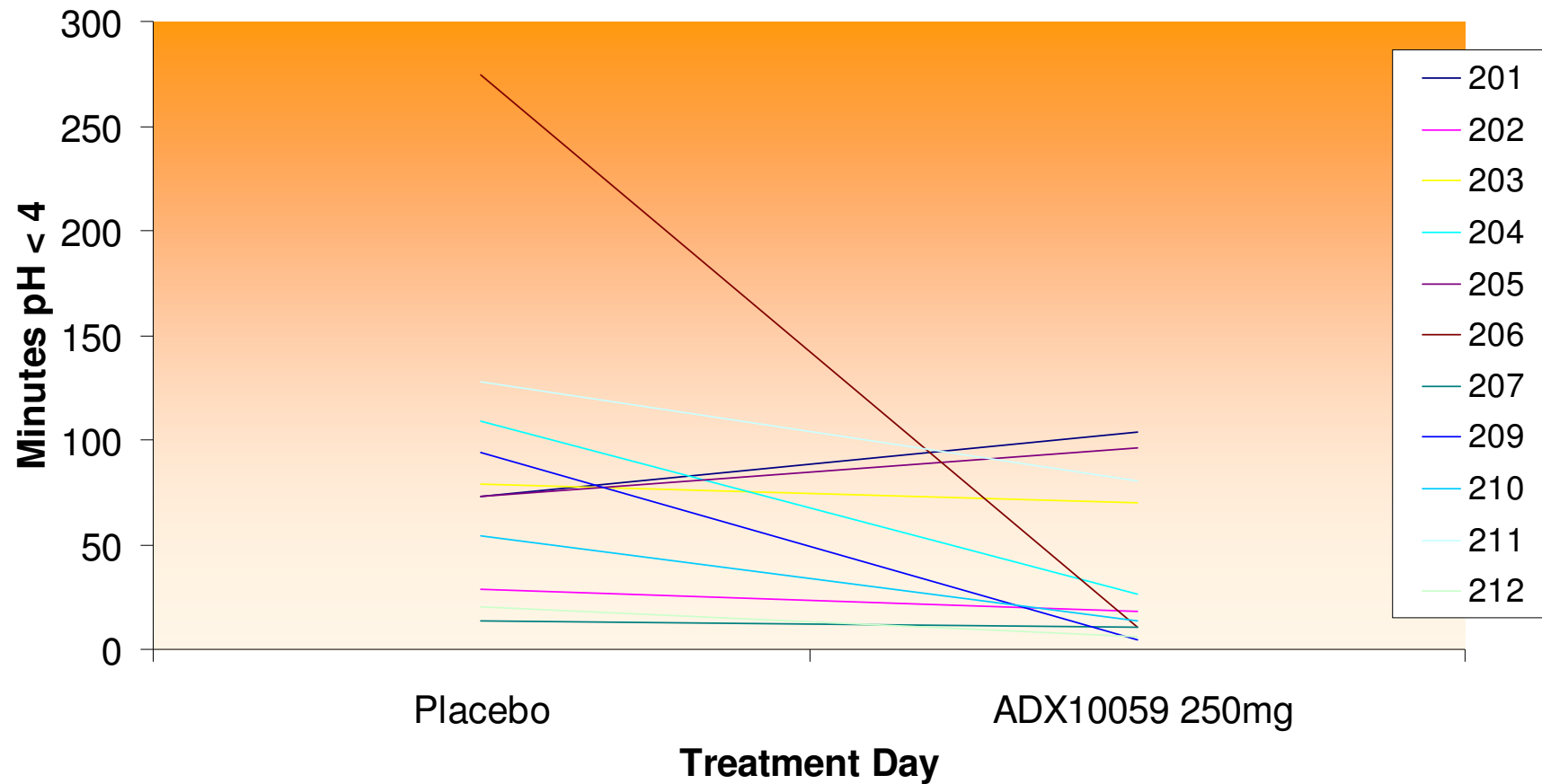


Efficacy Variable	ADX10059 250mg t.i.d N = 11	Placebo t.i.d. N = 11	P value
% time pH<4 in 24h	3.5	7.2	0.014
% time pH<4 nocturnal	3.7	9.7	0.0028
Median pH 24h	6.6	6.4	0.0015
Reflux pH<4 in 24h (n)	20.5	32.7	ns
Total duration reflux pH<4 24h (min)	40	86	0.0132
Reflux pH<4 nocturnal (n)	6.4	13.6	ns
Total duration reflux pH<4 nocturnal (min)	16.2	48.6	0.0021
No. episodes pH drop ≥ 1 24h	27.8	38.6	0.054
Longest duration pH drop ≥ 1 (min)	24.0	33.4	ns
No symptomatic episodes	1.9	7.0	0.031
Duration symptomatic episodes (min)	5.2	13.9	0.031

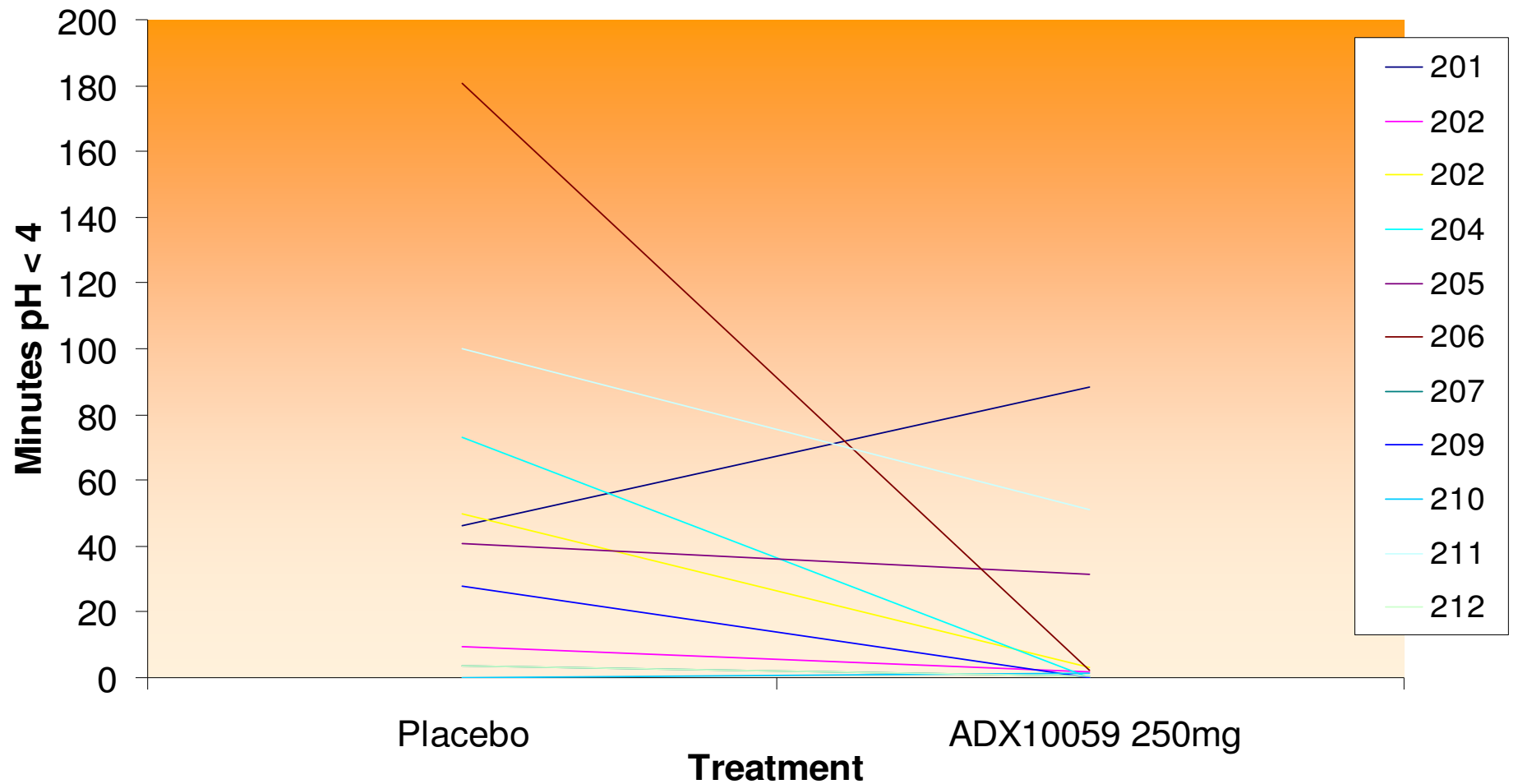
Mean (SD) total oesophageal acid exposure time



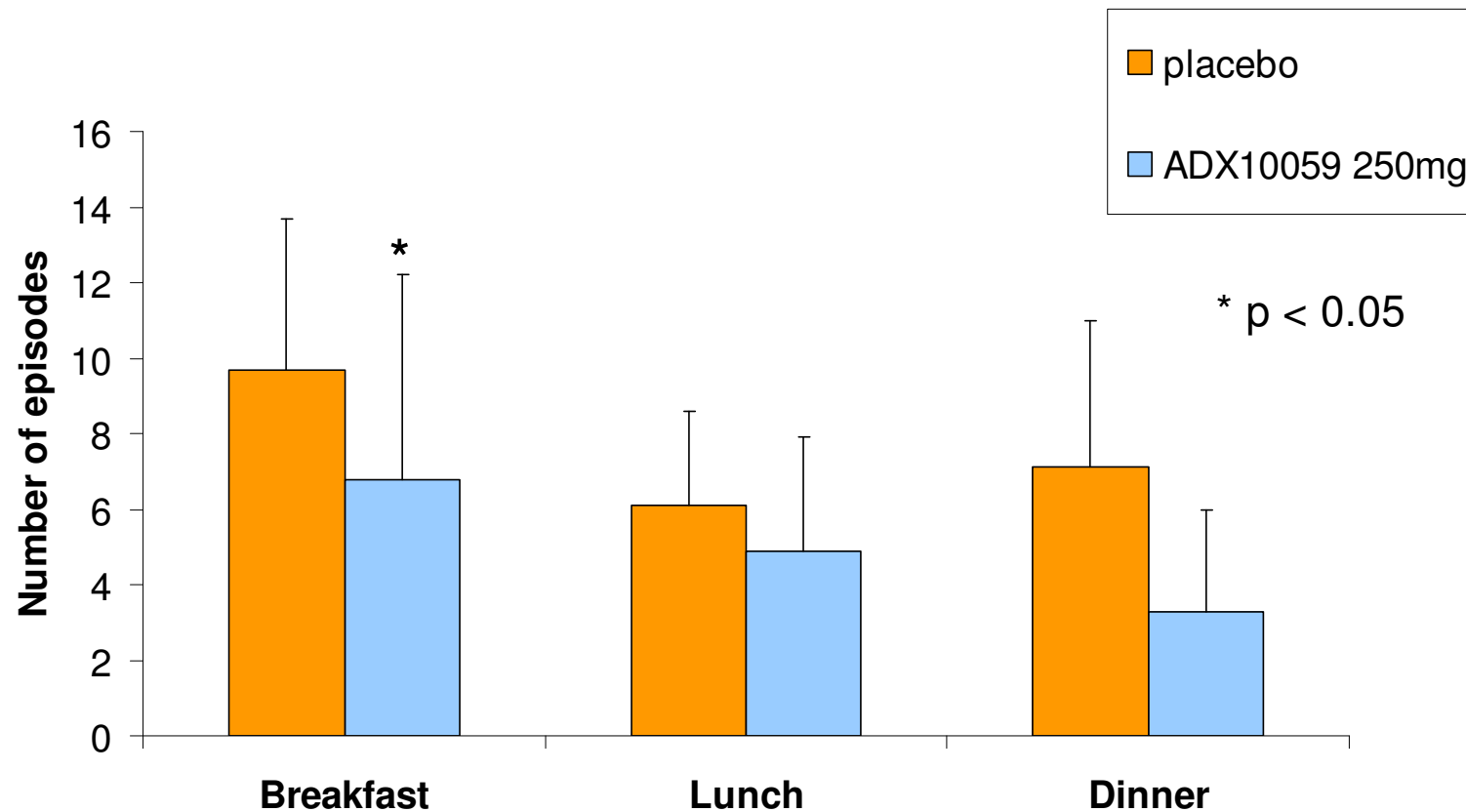
Individual 24h oesophageal acid exposure time



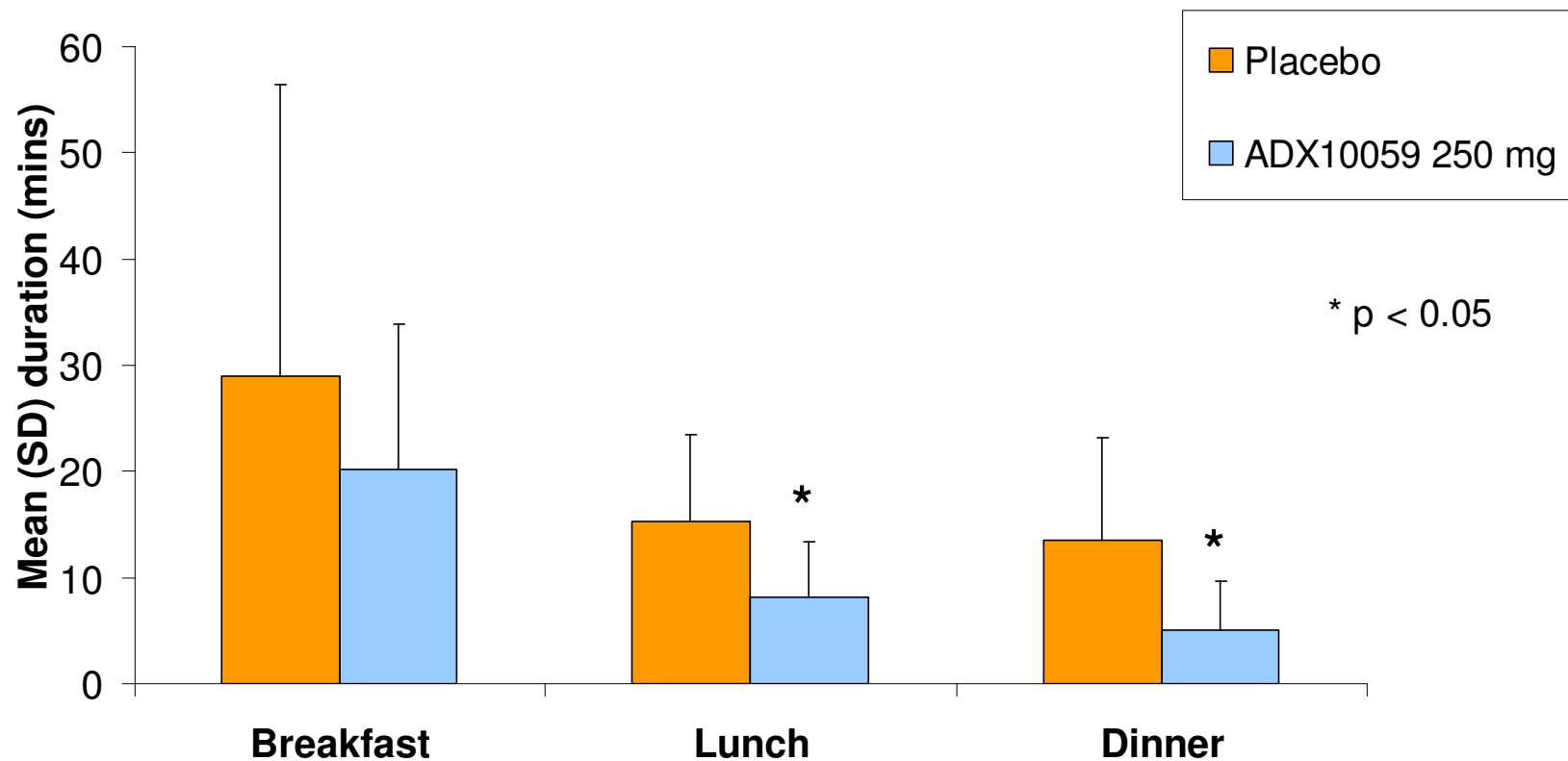
Individual nocturnal acid exposure time



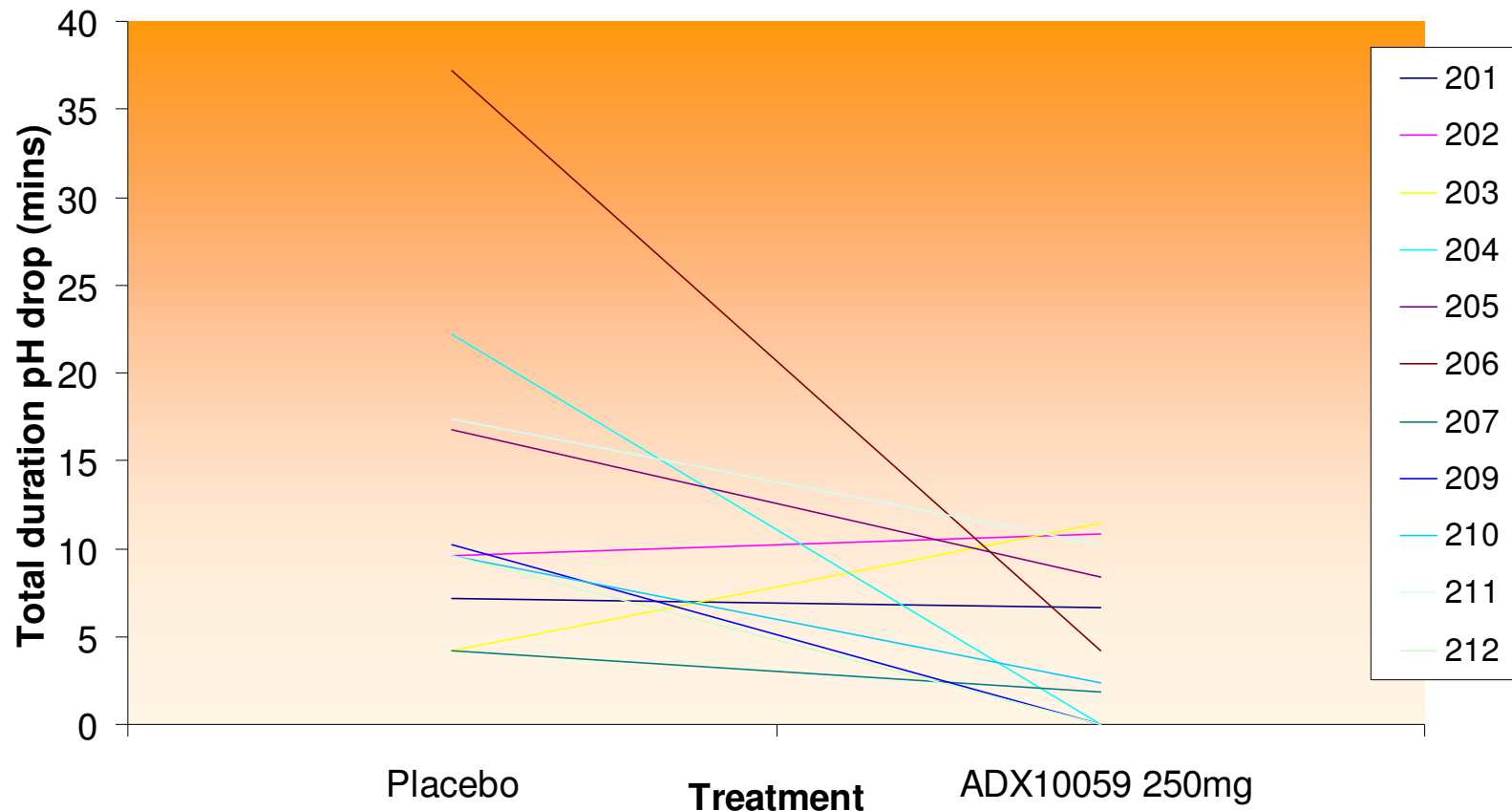
Mean (SD) number of episodes pH ≥ 1 in 4h post prandial periods



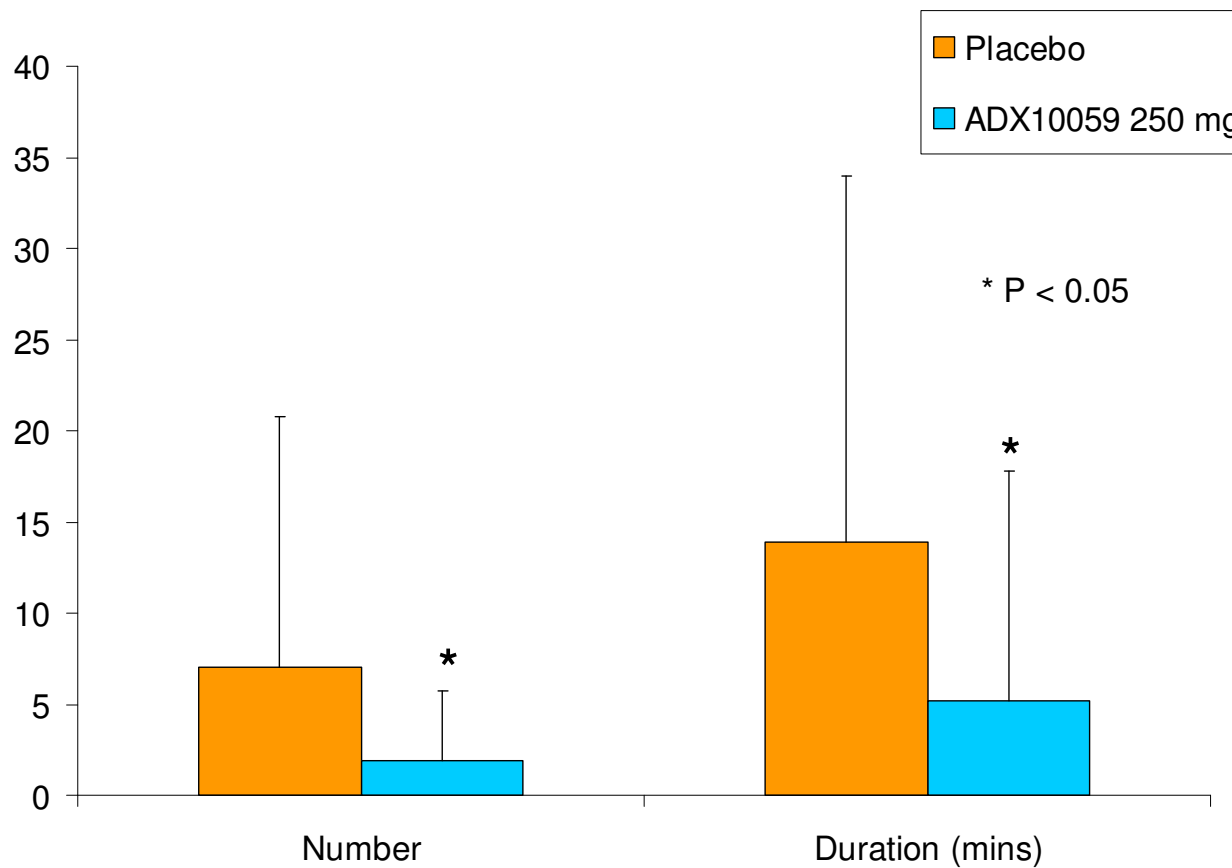
Mean (SD) total duration of pH drop ≥ 1 in 4h post prandial periods



Individual duration of pH drop ≥ 1 post dinner



Mean (SD) number and duration of symptomatic episodes



Safety and tolerability

- ◆ All safety monitoring parameters normal (ECG, haematology, biochemistry, BP and HR)
- ◆ Incidence of adverse events placebo 8%, ADX10059 50 mg t.i.d. = 17%, ADX10059 250 mg t.i.d. = 92%
- ◆ Patients in higher dose group (75%) experienced mild to moderate dizziness accompanied by nausea in 25%
- ◆ AEs due to very rapid absorption of ADX10059
 - Trial used unformulated drug in capsule
 - These effects can be avoided with formulation to slow rate of absorption

Conclusions

- ◆ First-in-man evidence of effect of mGluR5 NAMs in treatment of GERD
- ◆ ADX10059 50 mg t.i.d did not appear effective but large inter patient variability
- ◆ ADX10059 250 mg t.i.d. normalised 24 hour and nocturnal oesophageal pH
- ◆ ADX10059 250 mg t.i.d. reduced the duration of acid exposure in the post prandial and nocturnal periods
- ◆ Effects on reducing pH measured acid reflux were associated with a reduction in frequency and duration of clinical symptoms.
- ◆ Effects apparent on a single day of dosing.
- ◆ These results warrant further investigation of the utility of ADX10059 in the treatment of GERD



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