

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 bind to the receptor in a site other than the natural ligand binding site and either enhance (PAM) or reduce (NAM) activity of the natural ligand.
- Non competitive with natural ligand – “dimmer switch”
- mGluR5 in the stomach and OG junction, involved in regulating vagal control of LES function
- 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



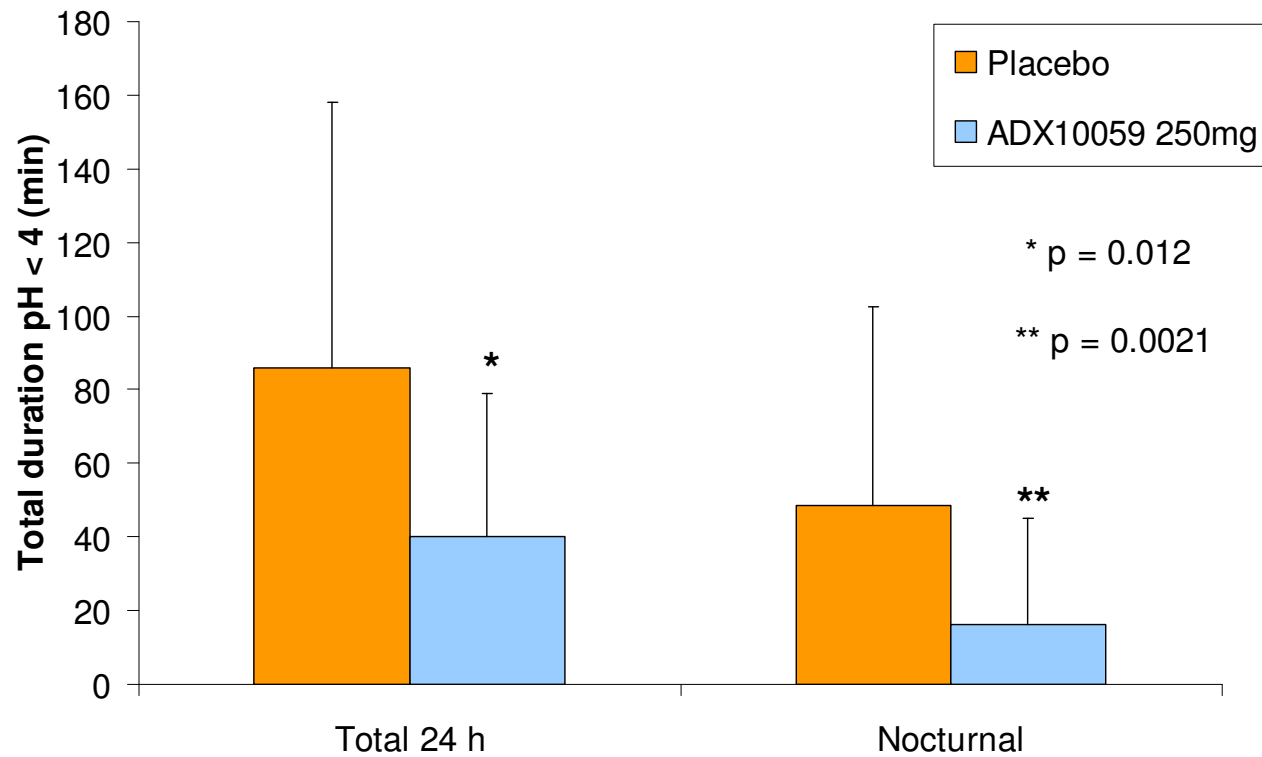
Treatment Group	% time pH < 4 in 24h	% time pH< 4 diurnal	% time pH < 4 nocturnal
Group 1 n = 12			
Placebo	14.9	9.5	22.7
ADX10059 50 mg	15.1	12.8	18.9
Estimate change from baseline	2.71	4.75	0.19
95% CI	[-2.05; 7.48]	[0.14;9.37]	[-5.88; 6.26]
P value	ns	0.0442*	ns
Group 2 n = 11			
Placebo	7.2	5.2	9.7
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

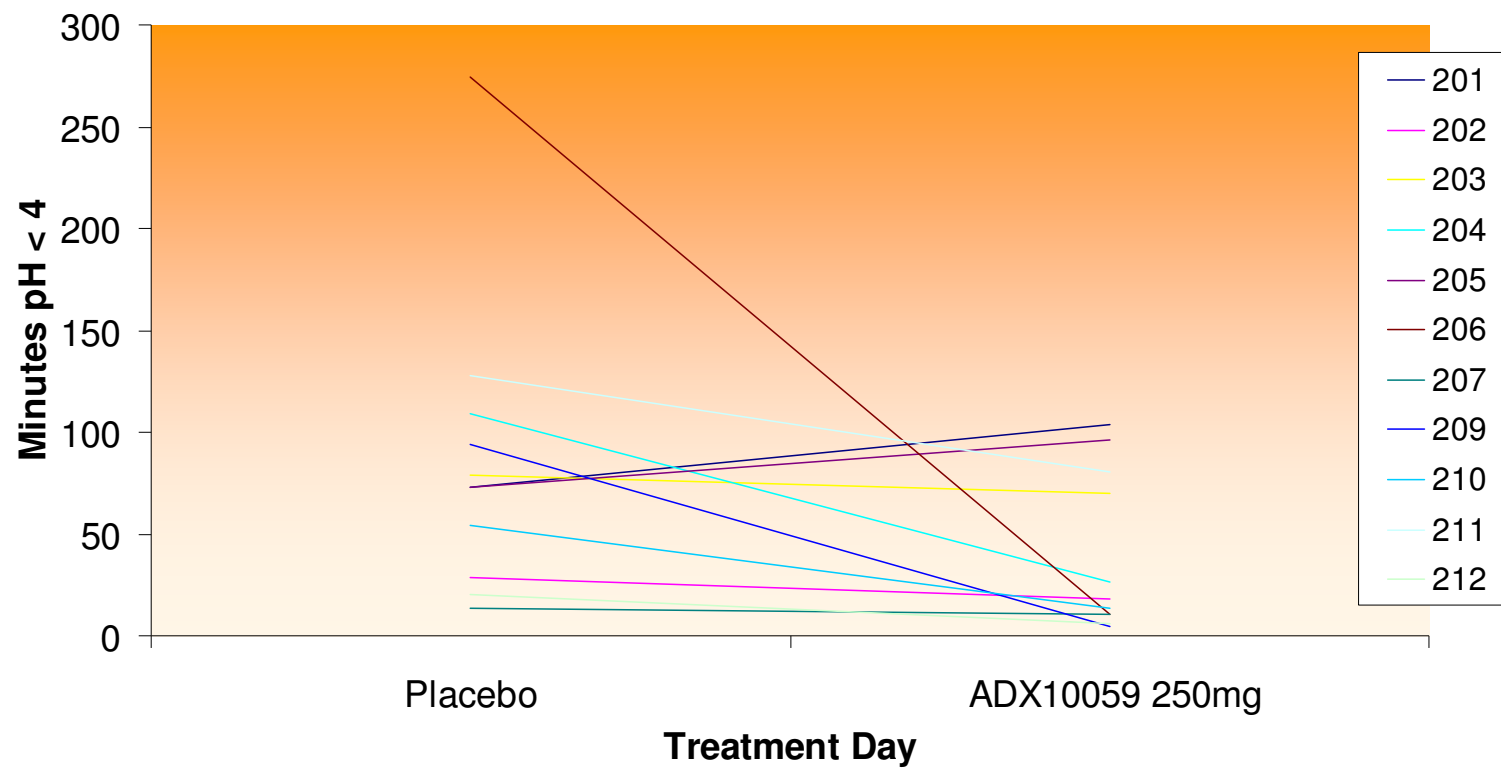


Efficacy Variable Mean (SD)	ADX10059 250mg t.i.d N = 11	Placebo t.i.d. N = 11	P value
Reflux pH<4 in 24h (n)	20.5 (19.4)	32.7 (20.3)	ns
Total duration reflux pH<4 24h (min)	40 (38.7)	86 (72.2)	0.0132
Reflux pH<4 nocturnal (n)	6.4 (9.9)	13.6 (12.3)	ns
Total duration reflux pH<4 nocturnal (min)	16.2 (29.0)	48.6 (54.0)	0.0021
Total duration of pH drop ≥ 1 24h (min)	118 (57)	75 (46)	0.054
Total duration of pH drop ≥ 1 nocturnal (min)	58 (42)	31 (34)	0.0049
No symptomatic episodes	1.9 (3.8)	7.0 (13.8)	0.031
Duration symptomatic episodes (min)	5.2 (12.6)	13.9 (20.1)	0.031

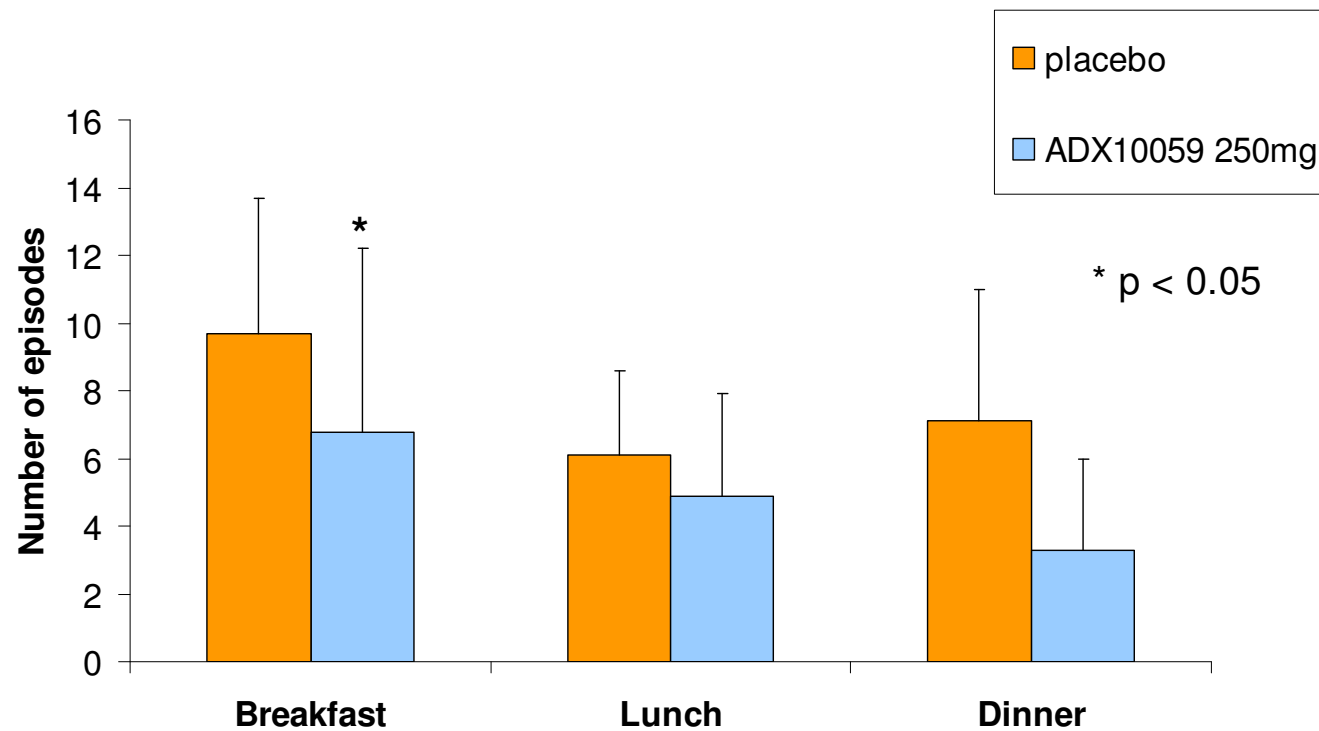
Mean (SD) total duration of reflux episodes



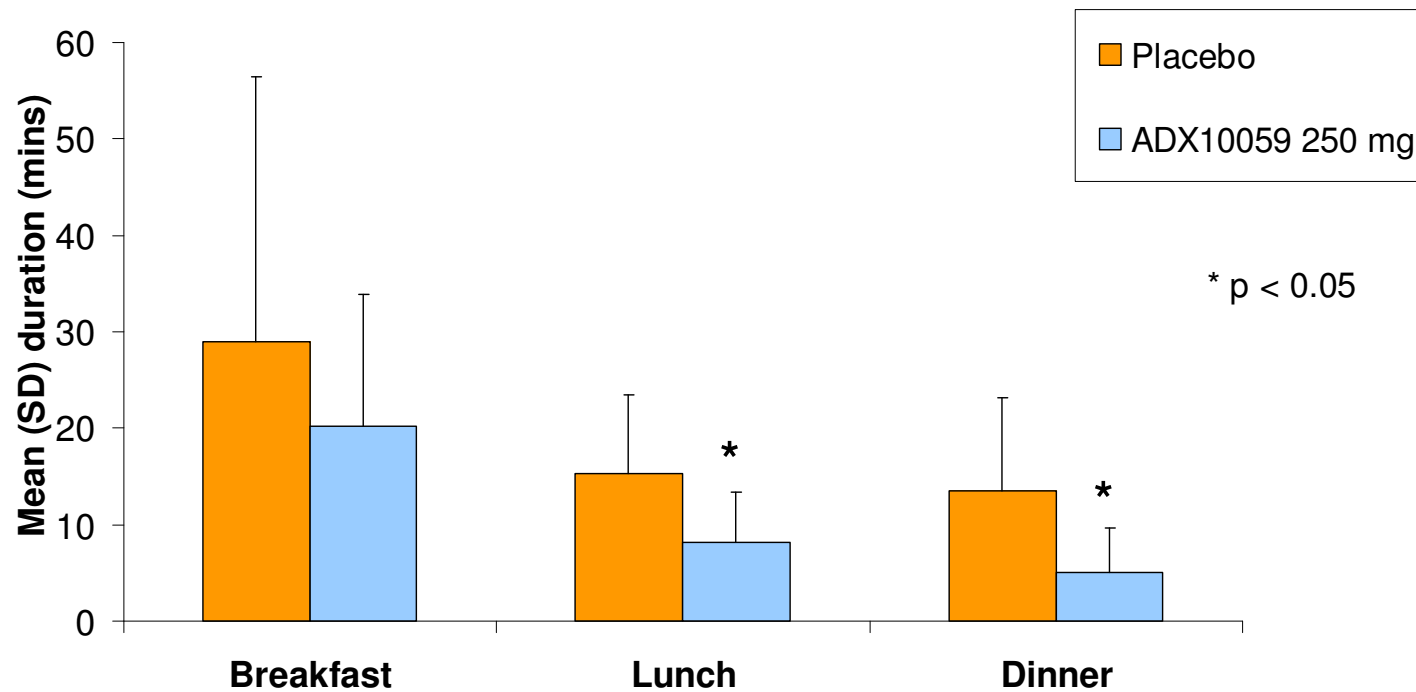
Individual total duration of reflux episodes (24h)



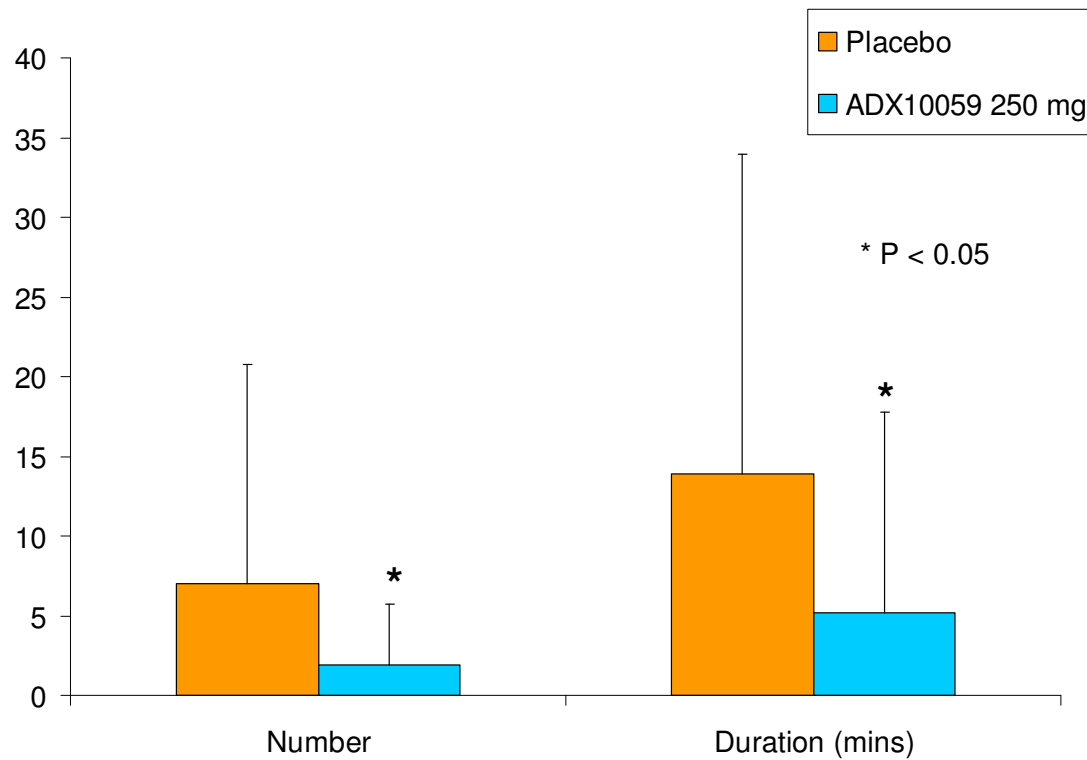
Mean (SD) number of episodes $\text{pH} \geq 1$ in 4h post prandial periods



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



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
 - Modified release formulation with slower rate of absorption, reduced C_{max} and improved tolerability currently in use for Phase 2B

Conclusions

- ◆ First-in-man evidence of effect of mGluR5 NAM 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 reflux 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.
- ◆ ADX10059 is undergoing further investigation for the treatment of patients with GERD