AMISELIMOD, A SELECTIVE S1P RECEPTOR MODULATOR IN CROHN'S DISEASE PATIENTS: A PROOF OF CONCEPT STUDY

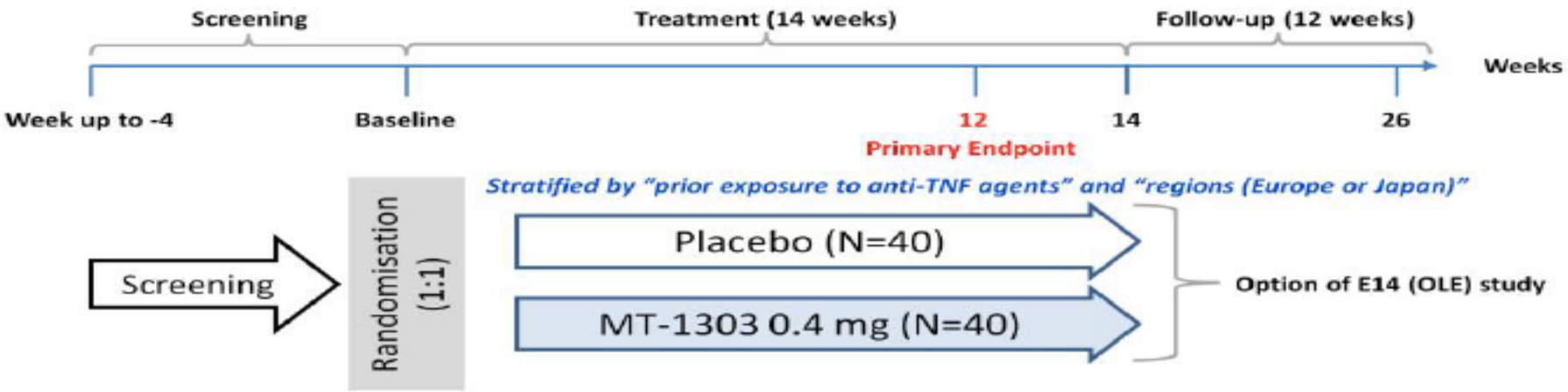
Geert D'Haens*, Silvio Danese, Martin Davies, Mamoru Watanabe, Toshifumi Hibi

*AMSTERDAM University Medical Centers

Amiselimod (AMS, MT1303)

- S1P receptors play an essential role in lymphocyte egress from the lymph nodes
- Fingolimod is an S1P modulator approved for the treatment of RRMS; toxicity includes cardiac arrythmia possibly due to modulation of both S1P1 and S1P3
- Other S1P modulators are under development for both UC and CD
- MT1303 has greater selectivity for S1P1 receptors not affecting S1P2 and S1P3
- MT1303 was effective in preclinical models of IBD, psoriasis, MS and SLE

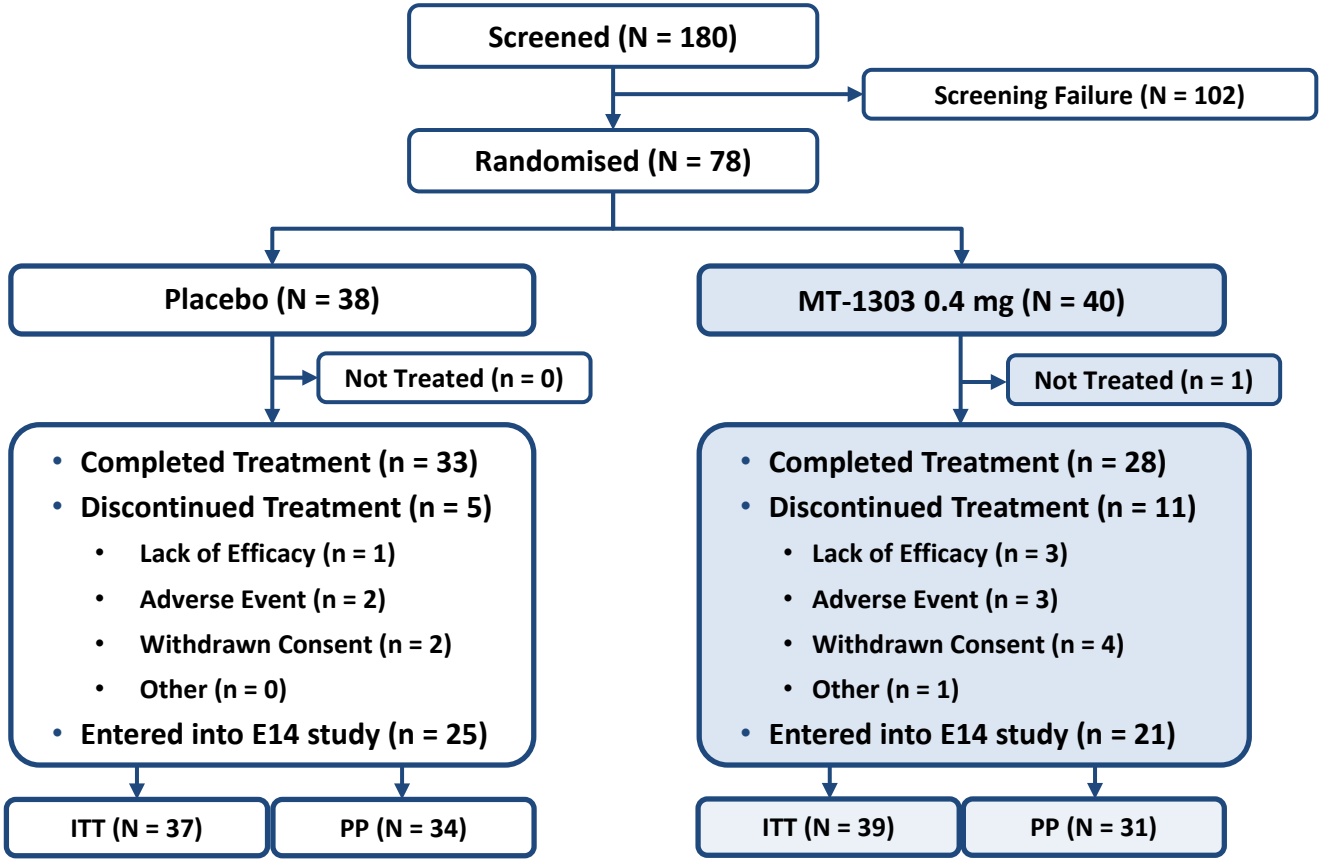
Study Outline



Study population:

- Patients (18-65 yrs old) with active Crohn's disease (CDAI 220-450)
- Previous use of Corticosteroids and/or IS and/or anti-TNF
- CRP ≥ 5 mg/l and/or faecal calprotectin ≥ 250 µg/g

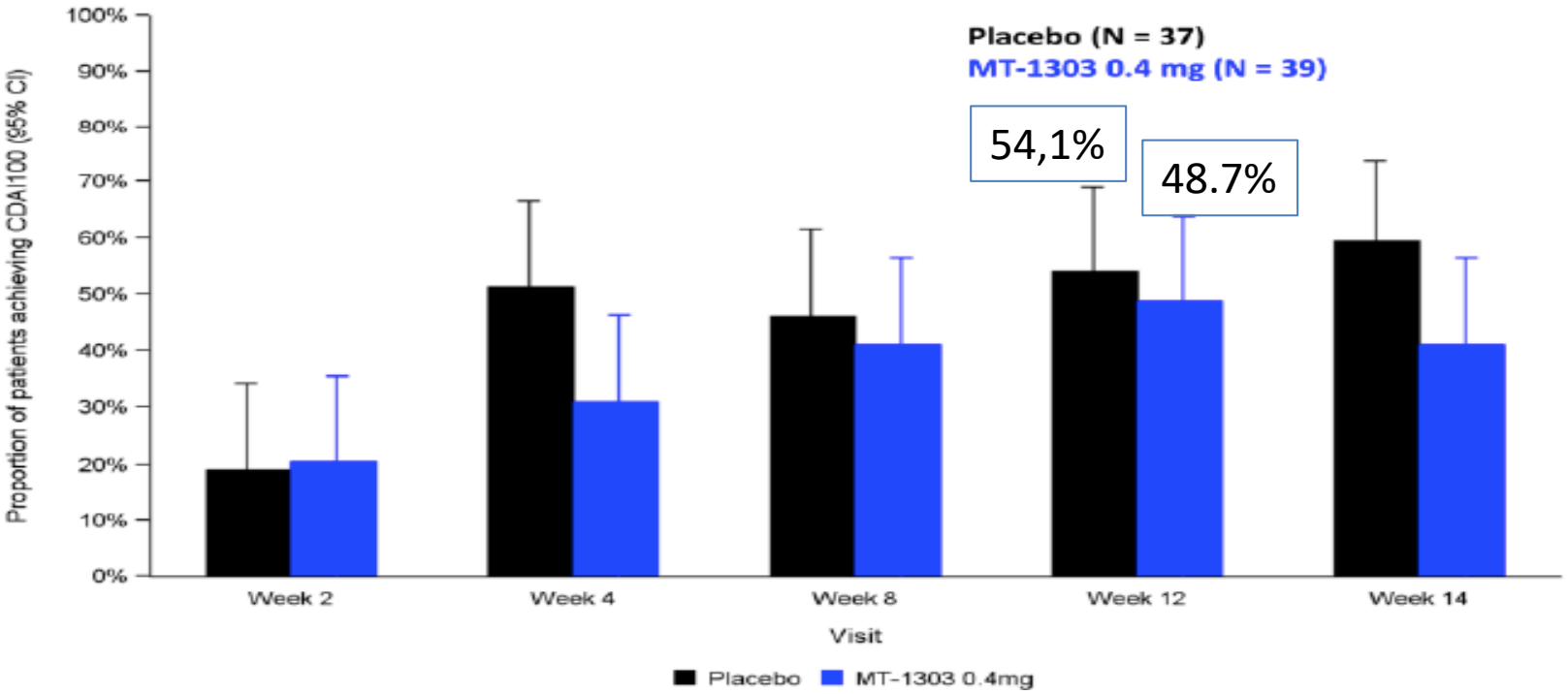
Patient Flow



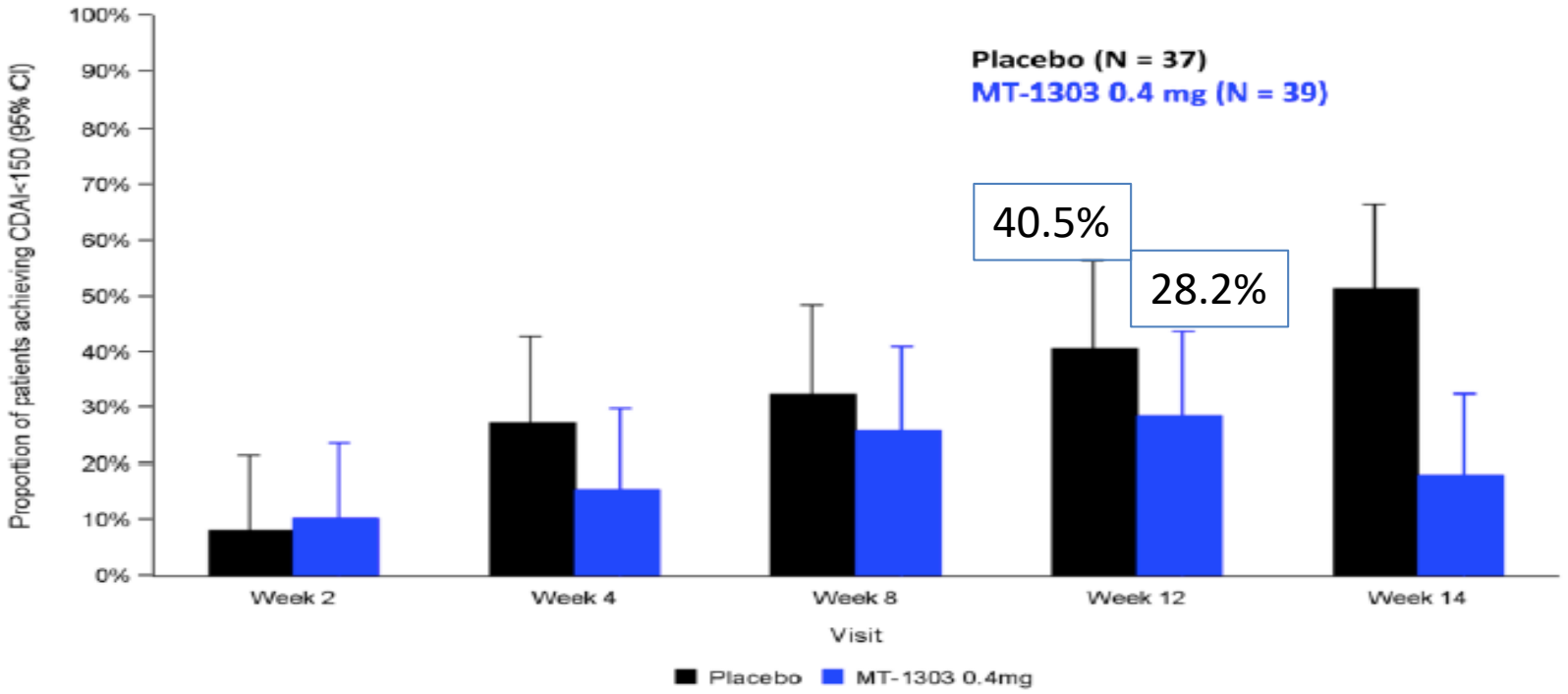
Patient Characteristics

	PLC (N=37)	MT-1303 (N=39)
Median Age (min,max)	31 (20,56)	34 (20,58)
Gender (% male)	64.9	59
Median CD Duration (yrs)(min,max)	6.86 (0.33,21.79)	8.25 (0.32,29.15)
CD Location ileitis/colitis/ileocolitis (%)	13.5/29.7/43.2	12.8/23.1/56.4
Prior use of TNF inhibitors (%)	24 (64.9)	22 (56.4)
Median CDAI at baseline	314 (202, 416)	301 (212,455)
Median CRP at baseline (mg/l)(min,max)	11.6 (0.32,68.80)	13.3 (0.22,172.00)
Median faecal calprotectine at baseline (µg/g)(min,max)	1713 (90,13637)	1390 (43,24307)
CRP/Faecal Calpro Categories n(%)		
CRP < 5 mg/l and FC ≥ 250 µg/g	12 (32.4%)	12 (30.8%)
CRP ≥ 5 mg/l and FC ≥ 250 µg/g	24 (64.9%)	25 (64.1%)
CRP ≥ 5 mg/l and FC < 250 µg/g	1 (2.7%)	2 (5.1%)

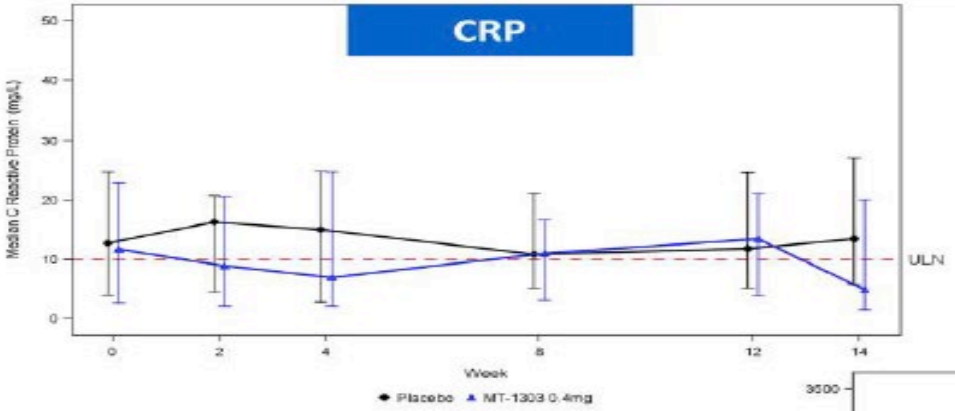
Primary Endpoint: week 12 CDAI 100 (NRI)

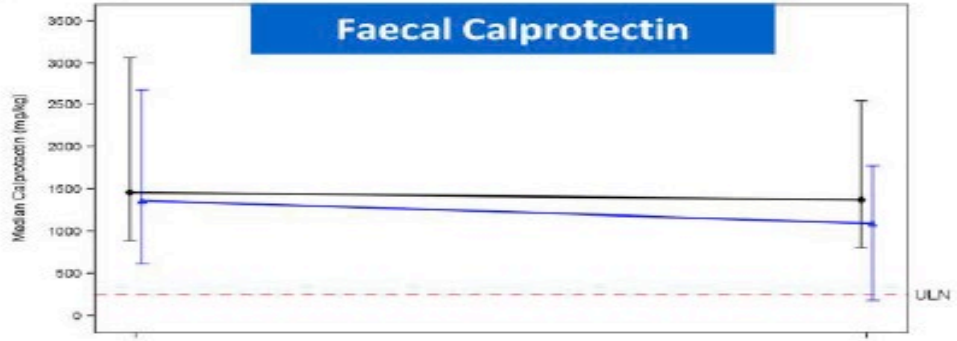


Secondary Endpoint: Remission (CDAI<150)

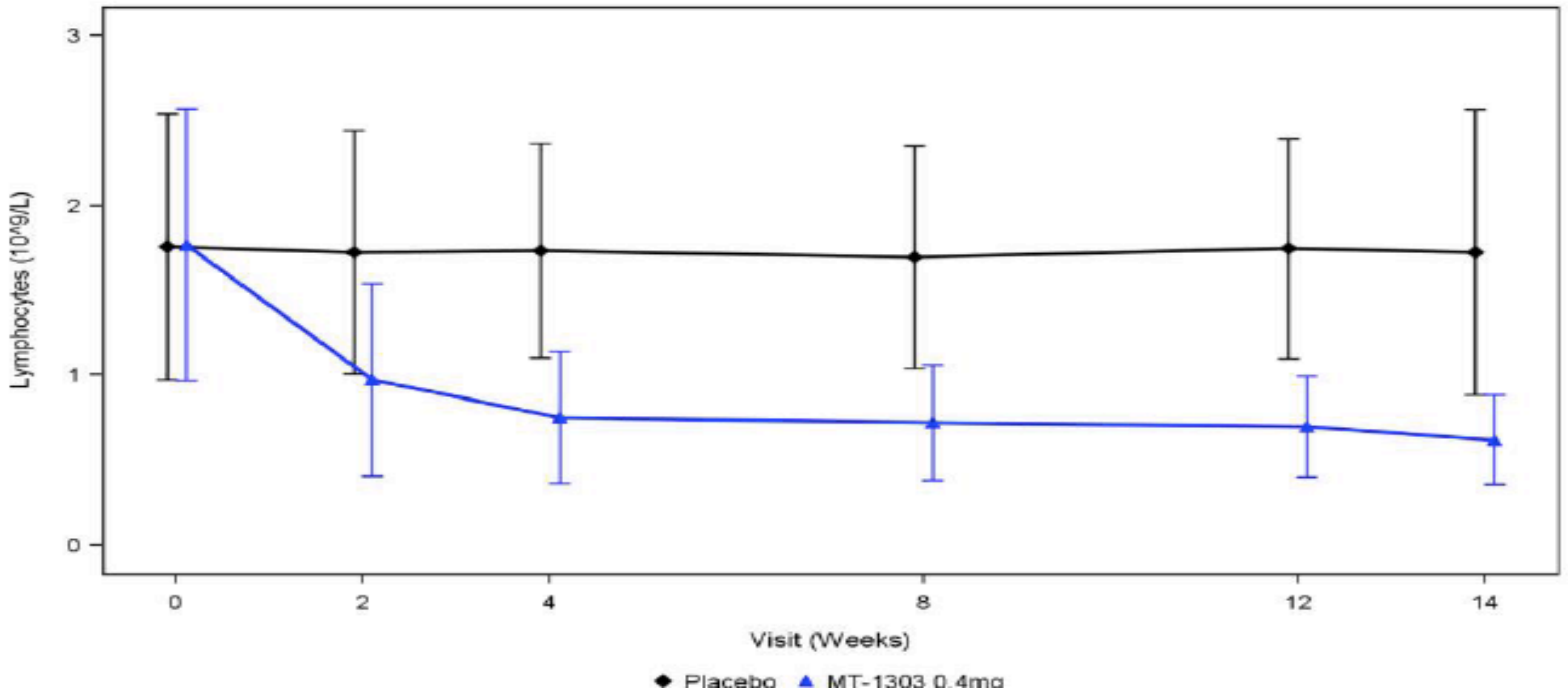


Biomarkers


CRP
Median C Reactive Protein (mg/L)
50
40
30
20
10
0
ULN
0
2
4
8
12
14
Week
Placebo
MT-1303 0.4mg


Faecal Calprotectin
Median Calprotectin (mg/kg)
3500
3000
2500
2000
1500
1000
500
0
ULN

PD: Mean PB Lymphocyte Counts



Note : this lymphocyte count reduction was considered weaker than observed in other indications and simulated data from MT-1303 Phase I studies.

Frequent TEAEs with Incidence of >5% (SAF) (1)

Frequent TEAEs (>5% by SOC/PT)	Placebo (N=38)	MT-1303 0.4 mg (N=39)	Overall (N=77)
	n (%)	n (%)	n (%)
Subjects with ≥1 TEAE	21 (55.3%)	26 (66.7%)	47 (61.0%)
Gastrointestinal disorders	8 (21.1%)	12 (30.8%)	20 (26.0%)
Crohn's disease	1 (2.6%)	6 (15.4%)	7 (9.1%)
Abdominal pain	1 (2.6%)	2 (5.1%)	3 (3.9%)
Diarrhoea	2 (5.3%)	0	2 (2.6%)
Infections and infestations	5 (13.2%)	10 (25.6%)	15 (19.5%)
Nasopharyngitis	2 (5.3%)	3 (7.7%)	5 (6.5%)
Nervous system disorders	6 (15.8%)	5 (12.8%)	11 (14.3%)
Headache	6 (15.8%)	4 (10.3%)	10 (13.0%)
Skin and subcutaneous tissue disorders	6 (15.8%)	5 (12.8%)	11 (14.3%)
Dermatitis allergic	0	2 (5.1%)	2 (2.6%)
Musculoskeletal and connective tissue disorders	6 (15.8%)	4 (10.3%)	10 (13.0%)
Arthralgia	3 (7.9%)	2 (5.1%)	5 (6.5%)
Back pain	2 (5.3%)	0	2 (2.6%)
Myalgia	0	2 (5.1%)	2 (2.6%)

n is the number of subjects. Percentages are based on the number of subjects in each treatment group. AE: Adverse event, SOC: System Organ Class, PT: Preferred Term, SAF Safety Population.

Frequent TEAEs with Incidence of >5% (SAF) (2)

Frequent TEAEs (>5% by SOC/PT)	Placebo (N=38)	MT-1303 0.4 mg (N=39)	Overall (N=77)
	n (%)	n (%)	n (%)
General disorders and administration site conditions	5 (13.2%)	2 (5.1%)	7 (9.1%)
Chills	2 (5.3%)	0	2 (2.6%)
Pyrexia	2 (5.3%)	0	2 (2.6%)
Reproductive system and breast disorders	4 (10.5%)	2 (5.1%)	6 (7.8%)
Dysmenorrhoea	2 (5.3%)	0	2 (2.6%)
Investigations	1 (2.6%)	4 (10.3%)	5 (6.5%)
Blood creatine phosphokinase increased	0	2 (5.1%)	2 (2.6%)
Blood and lymphatic system disorders	3 (7.9%)	1 (2.6%)	4 (5.2%)
Iron deficiency anemia	2 (5.3%)	0	2 (2.6%)
Cardiac disorders	1 (2.6%)	3 (7.7%)	4 (5.2%)
Injury, poisoning and procedural complications	2 (5.3%)	2 (5.1%)	4 (5.2%)
Eye disorders*	0	3 (7.7%)	3 (3.9%)
Respiratory, thoracic and mediastinal disorders	0	3 (7.7%)	3 (3.9%)
Oropharyngeal pain	0	2 (5.1%)	2 (2.6%)
Metabolism and nutrition disorders	2 (5.3%)	1 (2.6%)	3 (3.9%)

n is the number of subjects. Percentages are based on the number of subjects in each treatment group. AE: Adverse event, SOC: System Organ Class, PT: Preferred Term, SAF Safety Population.

Conclusions

- ✓ This was the first PLC controlled trial of an S1P inhibitor for the treatment of Crohn's disease
- ✓ This study did not assess mucosal changes but all patients had biomakers suggestive of active Crohn's disease
- ✓ Amiselimod 0.4 mg/d for 12 weeks was not superior to PLC for the induction of clinical response and remission
- ✓ High placebo response rate and weaker lymphocyte reduction were considered to contribute to the negative efficacy result in this study
- ✓ Treatment with AMS 0.4 mg was generally well tolerated and no new safety concerns related to AMS was reported in this study
- ✓ There were no clinically relevant toxicity signals