AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Tralokinumab (CAT-354)
Study Code	D2211C00001
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A Phase IIa, Randomised, Double-Blind, Placebo-Controlled, Parallel-Arm, Multicentre Study to Evaluate the Efficacy and Safety of Tralokinumab (CAT-354), a Recombinant Human Monoclonal Antibody Directed Against Interleukin-13 (IL-13), as an Add-On Therapy, on Clinical Response in Patients with Active, Moderate-to-Severe, Ulcerative Colitis

Study dates: First patient enrolled: 26 March 2012
Last patient last visit: 24 June 2013

Phase of development: Therapeutic exploratory IIa

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

For this study, patients were randomised from 30 sites in 6 European countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 summarises objectives and outcome variables.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the effect of tralokinumab compared with placebo in patients with active UC by assessment of clinical response, as defined by the Mayo score, at Week 8	Clinical response was measured as a decrease in Mayo score of ≥3 points from baseline, decrease in the total Mayo score from baseline ≥30%, and a decrease in the sub score for rectal bleeding ≥1 or absolute sub score for rectal bleeding of 0 or 1 point.
Secondary	Efficacy	To assess change in Mayo score from baseline to Week 8	Change in Mayo score from baseline to Week 8
	Efficacy	To assess mucosal healing at Week 8	Improvement of the endoscopy sub-score (from the Mayo score) from 3 or 2 to 0 or 1 point, or from 1 to 0 points
	Efficacy	To assess change in partial Mayo score from baseline to Week 4, 8, 12, 16, 20, and 24	Change in partial Mayo score from baseline to the different timepoints
	Efficacy	To assess the proportion of patients in clinical remission, as defined by the Mayo score, after 8 weeks	Proportion of patients in clinical remission, defined as Mayo score of 2 or lower with no individual sub-score exceeding 1 point
	Efficacy	To assess histology in biopsies from colonic mucosa at baseline and Week 8	Modified Riley score based on central assessment of biopsy samples
	Efficacy	To assess markers of disease activity and intestinal leakiness in serum and faeces at baseline, Week 4, 8, 12, 16, 20, and 24	Markers of disease activity : CRP (in serum) and calprotectin (in faeces) and marker of intestinal leakiness: Albumin (in serum)
	Pharmacokinetics (PK)/Safety	To assess the PK and immunogenicity of tralokinumab	C_{min} and AR of tralokinumab and incidence of anti-drug antibodies to tralokinumab in serum

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Safety	Safety	To evaluate the safety and tolerability of tralokinumab by assessment of reported Adverse Events (AEs), safety laboratory values, ECG, vital signs, weight, and physical examination findings	AEs, safety laboratory variables, ECG, vital signs (BP, pulse, and temperature), weight, and physical examination

Details of the exploratory objectives are mentioned in the clinical study report.
AR Accumulation Ratio; C_{min} Minimum Concentration BP Blood Pressure; CRP C-Reactive Protein; ECG Electrocardiogram; UC Ulcerative Colitis.

Study design

This was a Phase IIa, randomised, double-blind, placebo-controlled, parallel-arm, multicentre study to evaluate the efficacy and safety of 300 mg tralokinumab (CAT-354) (henceforth referred as tralokinumab) administered subcutaneously (sc). In addition to the Investigational Product (IP), all patients were to continue their background therapy for Ulcerative Colitis (UC) as per local standard of care.

A randomisation list was prepared using a validated computer program (GRand). Patients were randomised to the treatment with either tralokinumab or placebo in a ratio of 1:1. Randomisation to IP was done via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) at Visit 2.

The IP was handled by an unblinded IP manager/pharmacist at the study site and was administered by an unblinded study staff member who was not involved in the management or evaluation of study patients.

Target subject population and sample size

Non-hospitalised male and female patients aged 18 years to 75 years with active moderate to severe UC (baseline Mayo score of ≥6 including an endoscopy sub-score of at least 2), with endoscopically and histologically confirmed diagnosis at least 90 days prior to randomisation, were to be enrolled. Allowed background therapies included 5-aminosalicylic acid-containing medication, purine analogues, and low dose corticosteroids.

Assuming that the true proportions of patients responding were to be 65% and 35% in the tralokinumab and placebo arms, respectively, with a 1-sided test at $\alpha = 0.05$ and a power of 90%, 110 patients were planned to be randomised to yield 106 evaluable patients (53 patients in each treatment arm).

Investigational product and comparator: Dosage, mode of administration, and batch numbers

The details of IPs are given in Table S2.

Table S2 Details of investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number
Tralokinumab (CAT-354)	300 mg Formulated at a nominal concentration of 150 mg/mL in a sodium acetate buffer pH 5.5. The final formulation buffer consists of 50 mM sodium acetate, 85 mM sodium chloride, 0.01% (w/v) polysorbate 80, made up in water for injection.	MedImmune	ORD-LOT-4, ORD-LOT-5
Placebo	0.9% saline.	MedImmune	ORD-LOT-4, ORD-LOT-5

- Tralokinumab 300 mg was administered during study visits as 2 sc 150 mg injections every 2 weeks for 12 weeks starting from Visit 2 (Week 0).
- Placebo was administered during study visits as 2 sc injections every 2 weeks for 12 weeks starting from Visit 2 (Week 0).

Duration of treatment

Following a 21-day enrolment period, patients were randomised to a 12-week treatment period. Thereafter, patients entered a 12-week follow-up period (non-treatment).

Statistical methods

The significance level used for this study was 1-sided 5%. Model based point estimates were to be presented together with their 2-sided 95% Confidence Intervals (CIs), where appropriate.

The primary variable, clinical response at Week 8, and the secondary variables, mucosal healing and clinical remission at Week 8, were analysed using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the GCS-refractory status. Sensitivity analyses were performed excluding the patients with normal histology at baseline. Subgroup analyses were also performed on the primary variable.

Change from baseline to Week 8 in Mayo score and modified Riley score were analysed using the Analysis of Covariance (ANCOVA) and partial Mayo score was analysed using repeated measures analysis. Repeated measures analysis was also used to analyse the change from

baseline in markers of disease activity (C-Reactive Protein [CRP] and calprotectin) and the change from baseline in intestinal leakiness (albumin).

Tralokinumab serum concentrations were tabulated along with descriptive statistics and the incident of anti-tralukinumab antibodies was reported.

Safety variables were presented descriptively. All efficacy analyses were based on the full analysis set. Safety and Pharmacokinetics (PK) analyses were addressed using the safety analysis set.

Subject population

The disposition of patients in this study is summarised in Table S3. Of the 111 (75.5%) randomised patients, 55(98.2%) patients in the tralokinumab arm and 55(100.0%) patients in the placebo arm received treatment.

A total of 73 (65.8%) patients completed the treatment. The number of patients who completed treatment was numerically higher in the tralokinumab arm as compared with the placebo arm (38 [67.9%] and 35 [63.6%] patients in the tralokinumab and placebo arms, respectively). Seventeen (30.4%) and 20 (36.4%) of the randomised patients in the tralokinumab and the placebo arms, respectively, discontinued IP. The main reason for discontinuation of IP in both the treatment arms was development of study-specific discontinuation criteria (8 [14.3%] and 12 [21.8%] patients in the tralokinumab and placebo arms, respectively). The study specific criteria for discontinuation were insufficient therapeutic response requiring intensified medical therapy and insufficient therapeutic response necessitating surgical therapy.

The majority of patients participating in this study were White (108 [97.3%]) with a mean age of 41.5 years (range: 18 years to 70 years). There were 53 (47.7%) males and 58 (52.3%) females randomised into the study. The majority of patients (76 [68.5%]) were non-smokers.

The patient population was representative of the target population and the treatment arms were well-balanced with respect to demographic characteristics. There were numerical differences with regard to baseline disease characteristics between treatment arms which might indicate that the patient population in the tralokinumab arm had slightly more severe disease.

Table S3 Patient disposition (All patients)

	Number (%) of patients		
	Tralokinumab	**Placebo**	**Total**
Patients enrolled [a]			147
Patients randomised	56(38.1)	55(37.4)	111(75.5)
Patients who were not randomised			36(24.5)
Subject decision			2(1.4)

Table S3 Patient disposition (All patients)

	Number (%) of patients		
	Tralokinumab	**Placebo**	**Total**
Adverse event			2(1.4)
Subject lost to follow-up			1(0.7)
Eligibility criteria not fulfilled			28(19.0)
Other			3(2.0)
Patients who received treatment	55(98.2)	55(100.0)	110(99.1)
Patients who did not receive treatment	1(1.8)	0(0.0)	1(0.9)
Eligibility criteria not fulfilled	1(1.8)	0(0.0)	1(0.9)
Patients who completed treatment	38(67.9)	35 (63.6)	73(65.8)
Patients who discontinued treatment	17(30.4)	20(36.4)	37(33.3)
Subject decision	6(10.7)	6(10.9)	12(10.8)
Adverse event	2(3.6)	1(1.8)	3(2.7)
Development of study-specific discontinuation criteria	8(14.3)	12(21.8)	20(18.0)
Other[b]	1(1.8)	1(1.8)	2(1.8)
Patients who completed study	43(76.8)	37(67.3)	80(72.1)
Patients who discontinued study	13(23.2)	18(32.7)	31(27.9)
Subject decision	8(14.3)	13(23.6)	21(18.9)
Adverse event	2(3.6)	1(1.8)	3(2.7)
Development of study-specific withdrawal criteria	0(0.0)	1(1.8)	1(0.9)
Subject lost to follow-up	2(3.6)	2(3.6)	4(3.6)
Eligibility criteria not fulfilled	1(1.8)	0(0.0)	1(0.9)
Other[c]	0(0.0)	1(1.8)	1(0.9)

[a] Informed consent received.
[b] Visit 8 out of window period (data on file).
[c] Medical decision due to lack of efficacy (data on file).
Percentages for patients randomised are based on the number of patients enrolled; other percentages are based on the number of patients randomised.

Summary of efficacy results

The summary of clinical response at Week 8 is presented in Table S4. There was no statistically significant difference noted between the treatment arms with regard to the clinical response at Week 8 (percentage difference: 4.8, 95% CI: -13.0 to 22.5, p-value: 0.4062).

Twenty-one (37.5%) patients in the tralokinumab arm and 18 (32.7%) patients in the placebo arm achieved clinical response at Week 8.

Table S4 Summary of clinical response at Week 8 (Full analysis set)

			Comparison between groups		
Treatment group	**N**	**Number (%) of patients with response [a]**	**Estimate (%)**	**95% CI**	**p-value**
Tralokinumab	56	21 (37.5)	4.8	(-13.0, 22.5)	0.4062
Placebo	55	18 (32.7)			

[a] Patient was classified as a responder at Week 8 if all these 3 were criteria fulfilled: A decrease in the total Mayo score from baseline ≥3 points, decrease in the total Mayo score from baseline ≥30%, and decrease in the sub-score for rectal bleeding ≥1 or absolute sub-score for rectal bleeding of 0 or 1 point.

Estimate and 2-sided 95% CI presented together with a 1-sided p-value based on Cochran-Mantel-Haenszel (CMH) test with glucocorticosteroid-refractory status as stratification factor; patients with unknown glucocorticosteroid-refractory status were included in the 'No' glucocorticosteroid-refractory category.

CI Confidence Interval; N Number of Patients in the Treatment Arm.

There was no statistically significant difference noted between the treatment arms with regard to change in the Mayo score from baseline to Week 8 (difference in Least Square Mean [LS Mean]: -0.49, 95% CI: -1.63 to 0.65 and p-value: 0.3937).

Numerical improvement in mucosal healing at Week 8 was seen in the tralokinumab arm (18 [32.1%] patients) as compared with the placebo arm (11 [20.0%] patients). However, this difference was not statistically significant (percentage difference: 12.1, 95% CI: -4.0 to 28.3, p-value: 0.1043).

Numerical improvements were seen in the tralokinumab arm for all the weeks on treatment (Week 4, Week 8, and Week 12) for change from baseline in the partial Mayo score as compared with the placebo arm. Overall, the difference between the treatment arms for change from baseline in the partial Mayo score decreased over time. However, the results were likely to be biased by the increasing number of missing values over time; especially, considering a higher number of missing values in the placebo arm than the tralokinumab treatment arm. The maximum difference between the 2 treatment arms in the partial Mayo score was observed at Week 4 (LS Mean: -0.90, 95% CI: -1.76 to -0.04, p-value: 0.0406).

Numerical improvement was seen in the tralokinumab arm for the clinical remission at Week 8 (10 [17.9%] patients) compared with the placebo arm (3 [5.5%] patients). The difference between the arms was large (percentage difference: 12.4, 95% CI: 0.7 to 24.1, p-value: 0.0326).

There was no statistically significant difference noted between the treatment arms with regard to the change in the total modified Riley score from baseline to Week 8 (LS Mean difference: 0.25, 95% CI: -0.41 to 0.91 and p-value: 0.4490).

There were no consistent differences in change from baseline to any time point for CRP, albumin, and calprotectin between the tralokinumab arm and the placebo arm during the study.

Summary of pharmacokinetic results

The mean minimum concentration (C_{min}) of tralokinumab 300 mg SC administered once every 2 weeks (Q2W) at Visit 8 was 48.2 µg/mL (SD=27.3 µg/mL). Accumulation of tralokinumab exposure as assessed by C_{min} was observed; the mean accumulation ratio (AR) based on C_{min} from Week 4 to Week 12 was 1.28.

Overall, the PK properties of tralokinumab in UC patients were similar to those observed previously in asthmatics and healthy volunteers.

Summary of safety results

The mean duration of exposure was numerically higher in the tralokinumab arm (73.1 days) as compared with the placebo arm (68.3 days).

The number of patients experiencing Adverse Events (AEs) was similar in both the treatment arms (41 [74.5%] and 39 [70.9%] patients in the tralokinumab and placebo arms, respectively; Table S5). However, the number of AEs reported was more in the tralokinumab arm (240) as compared with the placebo arm (161); however, this difference originated to a large extent from a single patient in the tralokinumab arm, as patient E2801001 alone was reported to have experienced 67 AEs.

There was no death reported in the study. The number of patients experiencing Serious Adverse Events (SAEs) and Discontinuation of Investigational Product due to Adverse Events (DAEs) were similar for both the treatment arms.

Worsening of UC (colitis ulcerative) was the most commonly reported AE in the tralokinumab (14 [25.5%] patients) and placebo arms (15 [27.3%] patients) followed by headache (10 [18.2%] and (12 [21.8%] patients in the tralokinumab and placebo arms, respectively).

Table S5 Adverse events in any category (Safety analysis set)

	Number (%) of patients [a]	
AE category	**Tralokinumab (N=55)**	**Placebo (N=55)**
Any AE	41 (74.5)	39 (70.9)
Any AE with outcome = death	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	7 (12.7)	6 (10.9)
Any AE leading to discontinuation of IP[b]	8 (14.5)	10 (18.2)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Including patients discontinuing IP due to worsening of UC (In Table S3, patients with worsening of UC were included in study specific discontinuation criteria or in subject decision criteria)

This table includes AEs that occurred during entire study.

AE Adverse Event; IP Investigational Product; N Number of Patients in the Treatment Arm; SAE Serious Adverse Event.