AstraZeneca

Clinical Study Report	
Drug Substance	D9421-C
Study Code	D9421C00002
Edition Number	1
Date	8 October 2008

A multicentre, double-blind, randomised, parallel-group, Phase II study to assess efficacy and safety of D9421-C 9 mg and 15 mg versus placebo in Japanese patients with active Crohn's Disease

Study dates:	First patient enrolled: 16 October 2006 Last patient completed: 4 March 2008
Phase of development:	Therapeutic exploratory (II)
International Co-ordinating Investigator:	Not applicable to this study.

This study was performed in compliance with Good Clinical Practice.

Drug Product	D9421-C 3 mg capsule	**SYNOPSIS**	
Drug Substance	D9421-C		
Study Code	D9421C00002		
Edition Number	1		
Date	8 October 2008		

A multicentre, double-blind, randomised, parallel-group, Phase II study to assess efficacy and safety of D9421-C 9 mg and 15 mg versus placebo in Japanese patients with active Crohn's Disease

International co-ordinating investigator

Not applicable to this study.

Study centre(s)

This study was conducted at 21 centres in Japan.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	16 October 2006	Therapeutic exploratory (II)
Last patient completed	4 March 2008	

Objectives

The primary objective of this study was to evaluate the clinical efficacy of D9421-C 9 mg and 15 mg compared to placebo when orally given once daily to Japanese patients with mild to moderate active Crohn's disease affecting ileum, ileocecal region and/or ascending colon as defined by a score of ≥200 on the Crohn's Disease Activity Index (CDAI) by assessment of the remission after 8-week treatment defined by a CDAI score of ≤150.

The secondary objectives of this study were as follows:

1. To evaluate the clinical efficacy of D9421-C 9 mg and 15 mg compared to placebo when orally given once daily to Japanese patients with mild to moderate active Crohn's disease by assessment of the following variables:

- Remission (i.e. CDAI score of ≤150) after 2-week and 4-week treatment, change in CDAI score, time to the first remission, and clinical improvement defined by a remission (i.e. CDAI score of ≤150) or a decrease in CDAI score of at least 100 from Visit 2

2. To evaluate the safety of D9421-C 9 mg and 15 mg compared to placebo when orally given once daily to Japanese patients with mild to moderate active Crohn's disease by assessment of the following variables:

   - Morning plasma cortisol at pre treatment (Visit 2) and after 2, 4, 8 and 10 weeks of treatment, plasma cortisol level at adrenocorticotropic hormone (ACTH) test at pre treatment (Visit 2) and after 8 weeks of treatment

3. To evaluate the overall safety of D9421-C 9 mg and 15 mg when orally given once daily to Japanese patients with mild to moderate active Crohn's disease by assessment of the following variables:

   - Adverse events (AEs), laboratory variables (haematology, clinical chemistry, urinalysis), Electrocardiogram (ECG) and vital signs (pulse, blood pressure, body temperature)

4. To evaluate the change in disease specific health-related quality of life (HRQL) of D9421-C 9 mg and 15 mg compared to placebo when orally given once daily to Japanese patients with mild to moderate active Crohn's disease by assessment of the Inflammatory Bowel Disease Questionnaire (IBDQ) total score and all sub scores.

The exploratory objective of this study was to explore the population pharmacokinetics (PPK) of D9421-C 9 mg and 15 mg when orally given once daily to Japanese patients with mild to moderate active Crohn's disease by assessment of plasma budesonide concentration on Visit 2 and 4.

Study design

This was a multicentre, double-blind, randomised, parallel-group, phase II clinical study. Eligible patients were randomised to one of the three treatment groups listed below:

- D9421-C 9 mg once daily
- D9421-C 15 mg once daily
- Placebo once daily

Target patient population and sample size

Patients aged between 18 and 65 years with mild to moderate active Crohn's disease affecting ileum, ileocecal region and/or ascending colon, as defined by a score of ≥200 on the CDAI.

Totally 75 patients, 25 evaluable patients each in 3 groups (D9421-C 9 mg, 15 mg or placebo).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

- D9421-C 3 mg capsule

Patients randomised to D9421-C 9 mg or 15 mg took 5 capsules containing active ingredient or placebo in appropriate combination once daily before breakfast in the morning.

- D9421-C placebo capsule (matching D9421-C 3 mg capsule)

Patients randomised to placebo took 5 placebo capsules once daily before breakfast in the morning.

Duration of treatment

Treatment period: 8 weeks

After the treatment period or discontinuation of treatment, patients had two weeks of tapering.

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  - Remission after 8-week treatment defined by a CDAI score of ≤150
- Secondary variables:
  - Remission after 2-week and 4-week treatment
  - Change in CDAI score
  - Time to the first remission
  - Clinical improvement defined by a remission (i.e. CDAI score of ≤150) or a decrease in CDAI score of at least 100 from Visit 2

Patient reported outcomes (PROs)

- IBDQ total score and all sub scores

Pharmacokinetic

- Plasma budesonide concentration

Safety

- Morning plasma cortisol at pre treatment (Visit 2) and after 2, 4, 8 and 10 weeks of treatment
- Plasma cortisol level at ACTH test at pre treatment (Visit 2) and after 8 weeks of treatment
- AEs
- Laboratory variables (haematology, clinical chemistry, urinalysis)
- ECG
- Vital signs (pulse, blood pressure, body temperature)

Statistical methods

The rates of the remission and clinical improvement after 2, 4 and 8 weeks of treatment were summarised for each of the three treatment groups using a two-sided 90% confidence interval based on the Newcombe-Wilson score method. The Fisher's exact test was used for the comparison of the primary variable, which was the remission rate after 8 weeks of treatment, between D9421-C 9 mg and placebo. If this test rejected the null hypothesis that D9421-C 9 mg was equal to placebo, then the remission rate of D9421-C 15 mg after 8 weeks of treatment was to be compared with that of placebo using the Fisher's exact test for reference. The time to the first remission was analysed by a Kaplan-Meier method. Quantitative changes in the CDAI and IBDQ scores from Visit 2 were summarised for each of the three treatment groups using descriptive statistics.

Quantitative safety data were summarised for each of the three treatment groups using descriptive statistics. Qualitative safety data were summarised for each of the three treatment groups using frequency tables. Changes in the morning plasma cortisol concentrations and stimulated values of plasma cortisol after synthetic ACTH tests from Visit 2 were summarised for each of the three treatment groups using descriptive statistics.

Patient population

The first patient was enrolled to the study on 16 October 2006. The last patient completed the study on 4 March 2008.

A total of 90 patients were enrolled in the screening period and 77 (26, 25 and 26 in D9421-C 9 mg, 15 mg and placebo, respectively) patients were randomised and administered the study drug. Fourteen patients (18.2%) were prematurely withdrawn from the study treatment due to AE, voluntary discontinuation by patient, and others.

A total of 77 patients were included in safety analysis set and FAS, and 74 patients in PPS. The reasons for exclusion from PPS were major protocol deviations ("did not meet inclusion criteria" and "deviation from the restriction of allowed medications") with 3 patients.

For all the demographic and baseline characteristics, the three groups were well-balanced. Forty percent of the patients had colonic involvement. Ninety five percent of the patients used concomitant therapy (nutrition therapy, 5-ASA, etc) for Crohn's disease.

Pharmacokinetic results

In the PPK analysis, budesonide concentrations in plasma were well represented using a one-compartment model with first order absorption, but plasma concentrations around time for the maximum plasma concentration (t_{max}) were underestimated. Only patient status and treatment period were found as statistically significant factors on apparent volume of distribution (V/F). Systemic exposure in patients was 2.5 times higher than in healthy subjects at beginning of treatment with D9421-C and thereafter decreased to 70% of initial value within 2 weeks.

Efficacy results

Using FAS, remission rates at Week 8 were 23.1% for D9421-C 9 mg, 28.0% for 15 mg and 11.5% for placebo. The differences in remission rates between D9421-C and placebo were not statistically significant (p=0.4654 for D9421-C 9 mg vs. placebo and 0.1729 for D9421-C 15 mg vs. placebo). The results using PPS were similar to those using FAS. At Week 2, remission rates in the D9421-C groups were around 10% whereas no patient was in remission in the placebo group.

The decreases in CDAI total scores from baseline in D9421-C 9 mg and 15 mg were larger than in placebo (48.0±77.5, 58.2±84.7 and 27.2±89.9 [mean±SD] in D9421-C 9 mg, 15 mg and placebo, respectively). Clinical improvement rates for D9421-C 9 mg and 15 mg were higher than that for placebo throughout the treatment period. There were no clear differences in any of the efficacy variables between D9421-C 9 mg and 15 mg.

The remission rates at Week 8 in patients with colonic involvement were higher than that in patients with only ileum disease (33.3% and 50.0% versus 17.6% and 13.3% in D9421-C 9 mg and 15 mg, respectively).

Patient reported outcomes results

Total IBDQ scores at Week 8 were improved more in D9421-C 9 mg and 15 mg compared to that in placebo. Improvements in total IBDQ scores at Week 8 from baseline were 10.8±33.6, 23.2±24.6 and 6.5±29.4 (mean±SD) in D9421-C 9 mg, 15 mg and placebo, respectively.

Safety results

D9421-C 9 mg and 15 mg were safe and well tolerated during 8-week treatment when orally given once daily to Japanese patients with mild to moderate active Crohn's disease.

There were no deaths during the study. Four patients experienced a SAE during the study (2 each in D9421-C 9 mg (ileus, Crohn's disease) and placebo (perianal abscess, Crohn's disease). All of them were considered not drug-related except for perianal abscess in placebo. No SAEs were observed in D9421-C 15 mg.

There were 10 subjects who discontinued the study due to an AE in the study (6 [23.1%], 2 [8.0%] and 2 [7.7%] in D9421-C 9 mg, 15 mg and placebo, respectively). All of them were considered not drug-related except for 1 case in placebo.

The number of patients who had at least one AE was 19 (73.1%), 14 (56.0%) and 10 (38.5%) in D9421-C 9 mg, 15 mg and placebo, respectively. There were no severe AEs during the study except for 1 patient treated with placebo. Most commonly reported AEs (5% or over) in D9421-C group were Crohn's disease (5 [9.8%]), anaemia (5 [9.8%]), nasopharyngitis (5 [9.8%]), acne (4 [7.8%]), rash (3 [5.9%]), and pharyngolaryngeal pain (3 [5.9%]).

The number of patients who had at least one drug-related AE was 5 (19.2%), 8 (32.0%) and 3 (11.5%) in D9421-C 9 mg, 15 mg and placebo, respectively. The frequency of drug-related AEs in D9421-C 9 mg was lower than that in 15 mg.

The number of patients who had GCS-related AEs was 1 (3.8%) and 4 (16.0%) in D9421-C 9 mg and 15 mg, respectively. The reported GCS-related AEs were acne in 3 patients (2 D9421-C 15 mg and 1 D9421-C 9 mg), acne aggravated in 1 patient (D9421-C 15 mg) and moon face in 1 patient (D9421-C 15 mg). There were no patients who discontinued the study due to GCS-related AEs in the study.

No clinically important trends were noted in clinical laboratory tests, vital signs (pulse rate, blood pressure and body temperature) and ECG observations during the study.

Table S1 Summary/incidence rates (%) of adverse events (safety analysis set)

	D9421-C total n=51		**D9421-C 15 mg n=25**		**D9421-C 9 mg n=26**		**Placebo n=26**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Number of patients								
Any adverse events	33	64.7	14	56.0	19	73.1	10	38.5
Any serious adverse events	2	3.9	0	0.0	2	7.7	2	7.7
Any discontinuations of study due to adverse events	8	15.7	2	8.0	6	23.1	2	7.7
Any drug related adverse events *	13	25.5	8	32.0	5	19.2	3	11.5
Any severe adverse events	0	0.0	0	0.0	0	0.0	1	3.8
Any other significant adverse events	0	0.0	0	0.0	0	0.0	0	0.0
Number of events								
All adverse events	58		23		35		16	
All serious adverse events	2		0		2		2	

Table S1 Summary/incidence rates (%) of adverse events (safety analysis set)

	D9421-C total n=51		D9421-C 15 mg n=25		D9421-C 9 mg n=26		Placebo n=26	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
All discontinuations of study due to adverse events	8		2		6		2	
All drug related adverse events *	19		11		8		4	
All severe adverse events	0		0		0		1	
All other significant adverse events	0		0		0		0	

*: judged by the investigator.
Data derived from Table 11.3.2.1, Section 11.