AstraZeneca

BU-008-0005

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Entocort®, capsules

ACTIVE INGREDIENT: Budesonide

Trial title (number): A Fixed Versus Flexible Budesonide Dosing Schedule In Crohn's Disease For The Maintenance Of Remission (FREEDOM)

Developmental phase: IV
First subject recruited: 15 May 1996
Last subject recruited: 12 August 1999
Approval date: 15 July 2000

OBJECTIVES

Primary Objective

To determine the efficacy of a flexible versus fixed dosing schedule of oral budesonide CIR for the maintenance of remission from ileal or ileo-caecal CD, over a period of 12 months by comparing the percentage of treatment failures (See below)*.

Exhibited moderate or severe symptoms following treatment at dose level three for eight weeks.
OR
Were withdrawn from, or completed the trial with a CDAI (Crohn's disease activity index) greater than 200 and who exhibited moderate or severe symptoms.

Secondary Objectives

- To determine the proportion of patients who, having had their budesonide dose increased (9 mg o.m. for up to 8 weeks out of 52), remained in the study for the full twelve month period compared to the fixed dose group.
- To determine the average daily-prescribed budesonide dose for the fixed dose group compared to the flexible dose group.
- To determine the cumulative loperamide consumption for the flexible dose group compared to the fixed dose group.

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*Patients termed as treatment failures were those who;

- To determine the percentage of days on which patients were asymptomatic and had not consumed any loperamide in the fixed dose group compared to the flexible dose group.

METHODS

The study was a double blind, randomised, reference-controlled multicentre study, using a parallel group design.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Thestudy was carried out in patients in clinical remission from ileal orileo-caecal Crohn's disease. Thefollowing criteria were to have been fulfilled:

1. Inremission for at least a month exhibiting no symptoms or only mild symptoms.Patients must have received only stable or reducing doses of Crohn'sdisease medication within three months of entry.
2. At leastone episode of active disease within one year prior to entry documented by aclinic visit (not necessarily endoscopy) and an increase orinitiation of Crohn's disease medication.
3. Crohn'sdisease restricted to ileal/ ileo-caecal region and/or ascending colon. None ofthe following criteria were to have been fulfilled:

None ofthe following criteria were to have been fulfilled:

1. Anincrease in dose or the initiation of oral steroids or 5-ASA drugs within thethree months prior to study entry or an inability to stop treatment withany of these drugs at entry
2. Arequirement for parenteral or polymeric nutrition, cholestyramine,immunosuppresive agents at entry.
3. Patientswho have received treatment with immunosuppresive agents such as azathioprine,cyclosporin and mercaptopurine within 3 months prior to trial entry. Patientswho had received ketoconazole (Nizoral®)within seven days of entry.
4. Resectionof more than 100 cm of ileum; ileostomy. Patients who had achieved remissionby resective surgery and who have not since had an episode of active disease.
5. Otherbowel diseases e.g. coeliac disease, symptomatic stricture. Patients withCrohn's disease known to be associated with active fistulas and/or septiccomplications.
6. Distaldisease (past or present).
7. Patientsfor whom surgery was planned. Patients who were likely to require surgery forCrohn's disease in the next 12 months.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION
Budesonide (Entocort® capsules), dosage form, 3, 6 or 9 mg controlled ileal release (CIR) capsules, o.d., oral, manufactured by Astra Pharmaceutical Production AB, Sweden.

Test Product	Strength	Batch Numbers
Budesonide CIR	3 mg	VH 510/511/512 Expiry 8/97
Placebo for Budesonide CIR	For 3mg	VI 401 Expiry 5/97

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION
Budesonide (Entocort® capsules) dosage form, 6 mg controlled ileal release (CIR) capsules, o.d., oral, manufactured by Astra Pharmaceutical Production AB, Sweden.

Test Product	Strength	Batch numbers
Budesonide CIR	3 mg	VH 510/511/512; VK518; XM 563, 564; YD 1030; ZD 1085
Placebo for budesonide CIR	For 3mg	VI 401; YC 403; ZA 405

DURATION OF TREATMENT
12 months.

MAIN VARIABLE(S):

- EFFICACY
The primary variable was percentage of treatment failures as defined by moderate or severe symptoms following treatment at dose level 3 for 8 weeks or patients who were withdrawn from, or completed the study with a CDAI (Crohn's disease activity index) score >200 and who exhibited moderate and severe symptoms.

- **SAFETY**
Safety was assessed from adverse events recordings performed at each visit and from clinical chemistry and haematological blood tests.

STATISTICAL METHODS
The analyses were performed on an All Patients Treated basis. Life table analysis was used to compare the proportion of treatment failures up to one year after entry. Survival curves were compared between treatment groups by the log-rank test.

PATIENTS

	FLEXIBLE DOSE GROUP	**FIXED DOSE GROUP**	**Total**
No. planned	69	69	138
No. randomised and treated	68	75	143
Males/Females	28/40	28/47	56/87
Mean age (range)	42.1 (21-74)	42.5 (18-76)	42 (18-76)
No. analysed for efficacy	66	75	141
No. analysed for safety	67	75	142
No. completed/discontinued	35/31	39/36	74/67

RESULTS

- EFFICACY RESULTS
The results indicate that the treatment groups were well matched at entry with respect to disease history and patient characteristics. The primary efficacy variable was the percentage of treatment failures after 12 months

Table 1: Analysis of Treatment Failures

	Flexible Dose (n=66)	Fixed Dose (n=75)	P-value
Survival estimate of percentage of treatment failures	15%	19%	P=0.6075
Crude estimate of percentage of treatment failures (n/N)	12%(8/66)	15% (11/75)	P=0.8058

Median time to treatment failure could not be estimated for either group, as the survival estimates of the percentage of treatment failures were less than 50% in both groups. Time to first step-up to dose level 3 has been presented as a surrogate measure of relapse, where symptoms increased such that treatment at dose level 3 was required. In the flexible dose group the median time to step up was 287 days, fixed group 266 days. The time to first step-up to dose level 3 was not significantly different between groups (p=0.3709).

The percentage of patients who increased to dose level three during the study were 44% (29 patients out of 66) in the flexible dose group and 48% (36 patients out of 75) in the fixed dose group. The percentage of patients who completed the study after using dose level three was not significantly different between treatment groups. There was no significant difference between the two groups with respect to the average prescribed budesonide dose during the study. There was no evidence of a significant difference between the two groups with respect to the percentage of days on which loperamide was used. There was no evidence that the percentage of days on which no symptoms were experienced and no Loperamide was used was significantly different between groups.

SAFETY RESULTS

The number of adverse events was similar in the flexible and the fixed treatment groups. Laboratory variables were also similar at baseline and termination of the study between the two groups.

Table 3: Serious Adverse Events, discontinuations due to adverse events and other significant adverse events

	FLEXIBLE DOSE	FIXED DOSE
Deaths	0	0
Non-fatal serious AEs	19	14
Discontinuations of treatment due to AEs	9	4
Other significant AEs	10	7

Reference:

Green JRB, Lobo AJ, Giaffer M, Travis S, Watkins HC. Maintenance of Crohn's disease over 12 months: Fixed versus flexible dosing regimen using budesonide controlled ileal release capsules.Alimentary Pharmacology and Therapeutics 2001;15(9):1331-41.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Entocort™ (budesonide), Healthcare Professionals should view their specific country information.