CLINICAL STUDY REPORT

Efficacy of mesalazine 500 mg tablets in preventing relapses of quiescent Crohn’s disease in children
Multicentre, comparative, randomised, double blind, parallel group trial versus placebo

PENTACOMP/90/01

Investigational Product: Mesalazine, 500 mg tablets
Indication: Crohn’s disease in children – Prevention of relapses
Phase: III
Study Initiation Date: 09/02/1991
Study Completion Date: 08/01/2001

Name and Affiliation of Principal Investigator: 

Name and Address of Sponsor: 
FERRING France
7 rue Jean-Baptiste Clément
94250 - Gentilly - France
tel : +33 1 49 08 91 23, fax : +33 1 49 08 97 37,
email :

GCP Statement: This study has been performed in compliance with GCP.

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SYNOPSIS

<table>
<thead>
<tr>
<th>TITLE OF STUDY:</th>
<th>Efficacy of mesalazine 500 mg tablets in preventing relapses of quiescent Crohn’s disease in children</th>
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<td>INVESTIGATOR(S):</td>
<td>20 investigating centres, all paediatric departments specialised or not in gastroenterology. 18 sites were located in France, 1 in Belgium, and 1 in Switzerland.</td>
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<td>STUDIED PERIOD (YEARS):</td>
<td>(first patient first visit) : 09/02/1991 (last patient last visit) : 08/01/2001</td>
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<td>PHASE OF DEVELOPMENT:</td>
<td>III</td>
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<tr>
<td>OBJECTIVES:</td>
<td>Primary Objective: Assess relapse rate at 1 year associated with administration of Pentasa immediately after a flare-up of Crohn’s disease in comparison with administration of placebo</td>
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<td>METHODOLOGY:</td>
<td>Multicenter, prospective, randomised, controlled, double blind trial comparing administration of Pentasa, 50 mg/kg/day in 2 administrations per day, oral route, as preventive treatment of relapse in comparison with placebo in children with Crohn’s disease. The trial treatment was set up just after the end of curative treatment of a flare-up, and patients were randomised in 2 strata according to the treatment received for initial flare-up. Patients were treated for 12 months after initial flare-up curative treatment withdrawal, with a visit every 3 months during the trial treatment period.</td>
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<td>NUMBER OF SUBJECTS:</td>
<td>The number of children to be randomised was initially set at 30 per group, i.e 60 in total. Following results of the analysis performed on these patients, it was decided to randomise an additional set of 72 patients. In total, 137 patients were pre-included, 132 randomised, 122 in the Per Protocol Population.</td>
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<td>DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:</td>
<td>Both sexes, less than 20 years old, suffering from Crohn’s disease, with a diagnosis based on clinical, radiological, endoscopic and histological data, disease having started before the age of 15, jejunal, ileal and/or recto colic (with or without anal localisation) topography, in active phase, as defined by a score of at least 5 according to Harvey-Bradshaw scoring, with an assessment of lesions extension during a complete examination (colonoscopy, upper fibroscopy, small bowel series) performed with the 2 previous years.</td>
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<td>TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:</td>
<td>Mesalazine (Pentasa®), 500 mg tablets, oral route, 2 daily administration, daily dose = 50 mg/kg.</td>
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<td>Batch Numbers = RI 914T, RL 958T, SG 319T, TI 093T (First period of the study) ; DF 276T/CH 363, EC 331T/EC 441T, GA 538 T (2nd period of the study)</td>
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<td>DURATION OF TREATMENT:</td>
<td>12 months starting from withdrawal of all initial flare-up treatment.</td>
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<td>REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:</td>
<td>Placebo containing excipients only, strictly identical aspect. Batch numbers = SG 315T, RM 987 T1, RC 753 T (First period of the study), DF 276T/BG 347T, EC 331T/EC 442T, GA 538T (2nd period of the study).</td>
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CRITERIA FOR EVALUATION:

Efficacy: maintenance of clinical remission in patients after withdrawal of all treatments. The occurrence of a flare-up during the trial was defined as an Harvey-Bradshaw score ≥ 5, not associated with any identifiable intercurrent cause. Secondary efficacy endpoint: possibility to withdraw steroid treatment.

Safety: Adverse events occurrence, ECG monitoring, Biological monitoring for hepatic, renal and pancreatic parameters.

STATISTICAL METHODS:
Baseline characteristics were described using: % percentage, N total number of patients for qualitative items, mean ± standard deviation, N total number of patients for quantitative ones. Comparisons were performed using chi-square test or Fisher exact-test for qualitative items and: Mann-Whitney test for quantitative ones.

Time-to-event curves were compared using log-rank test: univariate analysis, proportional hazards model (Cox model): univariate and multivariate analyses with relative hazard ratio estimate ± standard error and with backward selection, if necessary, through likelihood ratio test.

Safety: description of Adverse Events and Serious Adverse Events, comparison of amylasaemia evolution using an ANOVA model, ECG presented as descriptive tables.

EFFICACY RESULTS: The assessment of a possible difference in treatment effect according to the stratum (medication or nutrition) and/or the period was the primary analysis.

Regarding the maintenance of remission (absence of relapse), whatever the statistical technique used, the “mesalazine medication period 1” group (N=17) has always the most favourable prognosis with the lowest rate of relapse and the “mesalazine nutrition period 2” (N=12) has always the most unfavourable prognosis with the highest rate of relapse. The “mesalazine nutrition period 1” (N=9) group is indistinguishable from placebo in one analysis (Cox model 2) and better than placebo in the other model (Cox model 1). The “mesalazine medication period 2 group” (N=18) and the 4 placebo groups (N=62) have an intermediate prognosis.

The same results have been demonstrated for failure.

For information, on the whole Per Protocol Population, 12 months after withdrawal, the rate of patients still in remission in the mesalazine group is 43 ± 7 % versus 37 ± 7% in the placebo group. Median time without relapse is 10.7 ± 2.1months in the mesalazine group versus 6.2 ± 1.8 in the placebo group. On the whole Per Protocol Nutrition Stratum Population, 12 months after withdrawal, the rate of patients still in remission in the mesalazine group is 33 ± 11 % versus 42 ± 12 % in the placebo group. Median time without relapse is 7.3 ± 1.8 months in the mesalazine group versus 8.9 ± 2.8 in the placebo group. On the whole Per Protocol Medication Stratum Population, 12 months after withdrawal, the rate of patients still in remission in the mesalazine group is 48 ± 9 % versus 35 ± 8 % in the placebo group. Median time without relapse is 11.5months in the mesalazine group versus 6.2 ± 2.5 in the placebo group.

SAFETY RESULTS: Regarding not serious adverse events, 32 patients (47.1%) in the mesalazine group and 29 patients (45.3%) in the placebo group reported at least one adverse event. 163 AE were reported (72 in the mesalazine group and 91 in the placebo group).

Most frequent AEs were headache, diarrhoea, abdominal pain, vomiting. These AEs were equally distributed between the groups.

Only a few AEs (in 1 patient (1.5%) for the mesalazine group and 2 (3.1%) in the placebo group) were considered by the investigators as related to treatment: alopecia, diarrhoea, anorexia and weight decrease in the placebo group, the 3 last AEs occurring for the same patient (N°136) ; abdominal pain in the mesalazine group.

One patient stopped prematurely the study medication in the placebo group and 2 in the mesalazine group due to AEs.

SAEs have been reported in 10 patients in the mesalazine group, hospitalisation for relapse of Crohn’s disease in 6 patients, hospitalisation for abdominal pain in 2 patients (with complete recovery) and occurrence of interstitial nephritis of unknown origin in the last one. 8 patients in the placebo group reported SAEs : 5 hospitalisations for Crohn’s disease relapse, one vagal malaise with complete recovery, one serum lipase and amylase levels increase, one interstitial pneumopathy.

The evolution of amylasaemia was not different between the two groups and was not significant within groups.
Regarding ECGs, no variation of ECG was reported in the mesalazine group when 2 patients in the placebo group had an ECG considered as normal at entry and an abnormal ECG when they stopped the study.

**CONCLUSIONS:** Efficacy results of this study are quite unclear, as the treatment effect varies with the period of recruitment of patients. Regarding safety, adverse events reporting was similar in placebo and mesalazine groups.