STUDY SYNOPSIS

Name of Company: Ferring-Leciva a.s..	Individual Study Table Referring to Part of the Dossier For Regulatory use only Volume:	(For National Authority Use only) For Regulatory use only
Name of Finished Product: Pentasa® Sachets 1 g		
Name of Active Ingredient: Mesalazine 1 g/ sachet	Page:	
Title of study: Multicentre, Controlled, Randomised, Open, Cross-over Study Comparing the Acceptability of Pentasa® Sachets versus Pentasa® tbl. 500 mg in Children with Crohn´s Disease **Study code: PENT-IBD-CH CZ**		
Co-ordinating Investigator: [redacted]		
Study centres: Multicentre Study (2 centres - Czech Republic)		
Studied period: Est. date of first enrolment: December 2004 Est. date of last completed: September 2005	**Phase of development:** IV	

Objectives:

Primary Objective:

To assess the acceptability of Pentasa® Sachets in comparisson with the reference Pentasa® tablets 500 mg in children with Crohn's disease.

Secondary Objectives:

- To compare the safety of both formulations of Pentasa®
- To compare the concentration of mesalazine and N-acetylmesalazine in urine and stool during the administration of both formulations of Pentasa®
- To compare the PCD activity index at Week 4 and 8

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Methodology:

Screening: At screening a complete medical history including family history of IBD and physical examination, including height, weight, blood pressure, pulse rate and evaluation of the major organ systems will be conducted. Basic haematology, serum chemistry and urine analysis and stool microbiology will be performed. PCD Activity Index will be calculated. All above mentioned tests must be performed maximum 7 days prior the baseline visit.

Visit No. 1: The study medication for next 4 weeks will be dispensed according to the randomisation scheme in common dose 2× 1 g of Pentasa® Sachets 1 g or Pentasa® tablets 500 mg. The patient diary will be distributed. If the laboratory assessment for faecal pathogens is found to be positive, the patients will be excluded from the trial.

Visit No. 2 (week 4 +/- 4 days): If the patient does not meet any criteria for premature withdrawal the following actions have to be taken: checking the diaries, calculation of the PCD Activity Index, urine examination, physical global assessment, blood and urine sampling and adverse events assessment. In 6 randomly selected patients from each group, stool and urine will be taken to assess concentrations of mesalazine and N-acetylmesalazine. The medication will be switched to the second formulation of Pentasa® (granules × tablets) and it will be dispensed for the next 4 weeks.

Visit No. 3 (week 8 +/- 4 days): The same evaluations as during Visit No. 2, calculation of returned medication. If the patient is withdrawn before week 8, the patient should be seen as soon as possible, and the date of this visit should be registered as the Visit No. 3. In 6 patients from each group who underwent the monitoring of mesalazine and N-acetylmesalazine concentrations during the Visit No. 2, the same evaluation as during Visit No. 2 will be performed.

Number of subjects (planned and to be analysed):

It was planned to include 50 subjects (25 per each group) + at least 4 subjects in the study. The final number of patients enrolled is much lower (29).

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Main criteria for inclusion:

Inclusion Criteria

To participate in this trial, patients had to meet all of the following criteria:

- Established diagnose of Crohn's disease
- Age 8–18 years, both sexes
- Weight above 40 kg
- Oral maintenance treatment with 5-ASA and any concomitant antinflammatory medication (maintained at the same dose during the study) before inclusion is permitted,
- written informed consent obtained (patient and his/her guardian)

Exclusion Criteria

- Patients with a history of allergy to salicylates
- Patients with known significant hepatic or renal function abnormalities
- Positive enteric pathogens in stool (Salmonela, Shigella, Yersinia, Campylobacter)
- Pregnant or lactating women
- Patients with a known history of disease, including mental/emotional disorder, that would interfere with their participation in the study,
- Patients who participated in another clinical study in the last 3 months,
- Patients who are unable to comply with the requirements of the protocol
- Patients who are unable to fill in the diary cards

Test product, dose and mode of administration, batch number:

Pentasa® 1 g Sachets., 2× 1 g per day, orally

Reference product, dose and mode of administration, batch number:

Pentasa® 500 mg tablets 2× 1 g per day, orally

Duration of treatment:

Both test and reference product were dosed for an 8 week period

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Criteria for evaluation:

Primary endpoint:

ACCEPTABILITY: Questionnaire (records in the patient diary) were used to evaluate the global acceptability of treatments.

Secondary endpoints:

PHARMACOKINETIC PARAMETERS:
Comparisson of 5-ASA and N-acetyl-5-ASA concentrations in urine and stool in children with Crohn's disease after the administration of Pentasa® Sachets/tablets
EFFICACY:
Clinical remission after 4 and 8 weeks of treatment, defined on the basis of or PCD activity Index
SAFETY: Safety variables were the occurrence of adverse events.
COMPLIANCE: The compliance was evaluated.

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Statistical evaluation:

Originally it was planned to perform the following statistical evaluation

Primary efficacy variables:

1) Global Assessment.

Average of 7 days values will be used.
The aim of the study will be to show the non-inferiority of Pentasa® sachets in Acceptability.
95 % CI for differences Pentasa® tbl – Pentasa® Sachets will be calculated.
The equivalence limit is given by 15 % of Pentasa® tbl mean.
The lower limit of CI for differences is to be higher than 15 %

2) 9 items of the questionnaire (Preparation of the drug, Appearance of the drug, Taste of the drug, Smell of the drug, Swallowing of the drug, Feelings after swallowing the drug, Eructation, Flatulence and Heartburn) are sumarised this way:

Average value of 7 days is calculated for each item
Sum of 9 items will be the second variable of Acceptability criterion. Non-inferiority of Pentasa® sachets will be evaluated in the same way as in 1).

Particular items differences will be analysed descriptively

Secondary efficacy variables:

1) Comparisson of concentrations of mesalazine and N-acetylmesalazine in urine and faecal water after administration of Pentasa® 1 g Sachets (2 g per day) and Pentasa® 500 mg tbl (2 g per day).

Concentrations in urine:
measurements before medication (0 h), 2 hours after medication, 4 h after, 6 hours. For Mesalazine (mg/l) and N-acetylmesalazine (mg/l) in each time 95 % confidence interval of the ratio (sachets/tablets) will be computed If confidence interval does not exceed (-0,8; 1,2) bioequivalence of Pentasa® sachets and tablets will be demonstrated

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Concentrations in feacal water:
For Mesalazine (mg/l) and N-acetylmesalazine (mg/l) in each time 95 % confidence interval of the ratio (sachets/tablets) will be computed If confidence interval doesn't exceed (-0,78; 1,22) bioequivalence of Pentasa® sachets and tablets will be demonstrated (refer to **Chyba! Nenalezen zdroj odkazů.**)

2) Comparisson of changes in PCD Activity index during treatments Pentasa® sachets – Pentasa® tbl.

Analysis of covariance with repeated measures adjusted on the baseline (PCD index before start of treatment) will be computed. Difference between sachets and tablets adjusted to baseline will be estimated and tested for significance.

Safety
Number of patients with any adverse event during tablets – sachets treatment will be compared. Fisher's exact test will be used. All adverse events will be documented in detail.

As the number of subjects enrolled was much lower (29 instead of 54 planned) the hypotheses tested are only informative. So, outputs from statistical analyses, both primary and secondary, could be evaluated at most as descriptive ones.

Date of the protocol: Final version, December 1, 2003

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Summary of study results:

In this Multicentre, Controlled, Randomised, Open, Cross-over Study the Acceptability of Pentasa® Sachets versus Pentasa® tbl. 500 mg in Children with Crohn´s Disease was compared. Originally it was planned to enrol 54 subjects, but the study was closed after the enrolment of 29 patients. Due to patient compliance only 26 subjects were analysed in the Per Protocol Population. As a result the statistical evaluation was not performed as planned but only presented as descriptive statistics.

For the primary efficacy endpoint *Acceptability* of the sachets non-inferiority was confirmed for the use of sachets, even only descriptive.For the secondary efficacy parameter *Measurement of Mesalazine oin plasma, urine and stool water* equal amounts of drug was found in the samples from both treatments. For plasma confidence intervals for proportion were not out of limits (-0.8; 1.2) so bioequivalence of Pentasa® sachets and tablets is demonstrated. For the other secondary efficacy endpoint *Comparison of changes in PCD Activity index during treatments* no significant differences between PCD scores between visits and treatments were observed.

In the study one serious adverse event were reported which was not related to the treatment with Pentasa® tablets or sachets. Due to small sample size and, thus, small number of adverse events of the trial, no significant effect of treatment duration on frequency of adverse events was found on the 5% significance level.