SYNOPSIS

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Title of the study:	Nolpitantium besylate in patients with mild to moderate Ulcerative Colitis. A double-blind, placebo-controlled efficacy and safety, 8-week study (NICE)
Investigators:	[redacted]
Study centers:	48 active centers located in 15 countries worldwide (Argentina, Chile, Belgium, Brazil, Canada, Czech Republic, Estonia, Hungary, Italy, Russia, Singapore, Malaysia, South-Africa, Spain, Sweden)
Publications (reference):	None
Study period: **Date first patient enrolled:** 28 April 2005 **Date last patient completed:** 21 September 2006	**Phase of development:** 2b
Objectives:	***Primary objective*** To evaluate the efficacy on clinical symptoms of 2 doses (1800 mg and 600 mg per day) of SR140333B, in patients with mild to moderate, treatment [5-aminosalicylic acid (5-ASA) or sulphasalazine]-resistant, ulcerative colitis (UC), on top of this treatment compared to placebo. ***Secondary objectives*** • To evaluate the effect of SR140333B on endoscopic appearance of the colonic mucosa, • To evaluate the efficacy of SR140333B on abdominal pain reduction, • To evaluate the effect of SR140333B on histological appearance of the colonic mucosa, • To evaluate the safety of SR140333B.
Methodology:	Multicenter, randomized, double-blind, placebo-controlled study with a parallel group design
Number of patients Evaluated:	Planned: 300 Randomized: 307 Treated: 306 Pharmacokinetics: 306 Efficacy: 306 Safety: 306
Diagnosis and criteria for inclusion:	Male or female patients of a least 18 years of age, with 5-ASA or sulphasalazine resistant mild to moderate UC of at least 6 months duration despite a stable dose of 5-ASA or sulphasalazine of at least 2 g/day for at least 4 weeks defined by a Disease Activity Index (DAI) from 6 to 10, including a clinical Mayo score of at least 4 and a bleeding score of at least 1.
Investigational product: Doses: Administration: Batch numbers:	SR140333B (capsules of 200 mg) 200 mg tid (ie, 600 mg/day) or 600 mg tid (ie, 1800 mg/day) Oral in fasting conditions (30 minutes before a meal) [redacted]
Duration of treatment:	8 weeks **Duration of observation:** 11 weeks, including an 1-week baseline period, an 8-week treatment period, and a 2-week follow-up period

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Reference therapy:	Placebo (matching capsules)
Dose:	Not applicable
Administration:	Oral in fasting conditions (30 minutes before a meal)
Batch numbers:	[redacted]

Criteria for evaluation:

Efficacy:

Primary efficacy variable: Clinical remission at Week 8

Clinical remission was defined by the combined presence of a clinical Mayo score lower than or equal to 1, a total absence of rectal bleeding, and no initiation of rescue therapy for lack of efficacy.

Secondary efficacy variables:

Key variables: Clinical response at Week 8, endoscopic Mayo score change from baseline to endpoint, endoscopic remission at endpoint.

Other variables: Stool frequency score, rectal bleeding score, Physician's global assessment score, Clinical Mayo score, DAI of the Mayo score, abdominal pain intensity assessed using a visual analogical scale, Geboes histological score.

Safety:

Overall clinical safety: clinical examinations, reporting of adverse events (AEs) throughout the study,
Laboratory safety (hematology and biochemistry parameters),
Vital signs (blood pressure and heart rate),
Electrocardiograms (12-lead ECGs).

Pharmacokinetics:

Plasma levels of SR140333 on Day 7, before and 1.5 hour after the morning dose, and on Day 56 (or at the end-of-treatment visit if premature discontinuation) before the morning dose.

Statistical methods:

Efficacy:

All efficacy analyses were performed on the intention-to-treat population.

Primary analysis

The clinical remission at Week 8 for each SR140333B dose was compared to placebo using the Cochran-Mantel-Haenszel statistic with the baseline use of steroids (Yes/No) as stratification factor. The Mantel-Haenszel estimate of the common relative risk (i.e. stratum-adjusted relative risk) for the clinical remission at Week 8 was provided, as well as the relative risk within each stratum.

Main secondary analyses

- The clinical response at Week 8 and the endoscopic remission at endpoint were analyzed in the same way as clinical remission at Week 8,
- The endoscopic Mayo score changes from baseline to endpoint were compared between groups using a two-way analysis of covariance with treatment group and baseline use of steroid as fixed effects, and baseline as covariate. Throughout this model, each dose of SR140333B was compared to placebo using appropriate contrast.

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Safety:	The safety evaluation was based upon the review of the individual values (clinically significant abnormalities) and descriptive statistics. Treatment-emergent adverse events (TEAEs) were summarized by treatment groups.
Pharmacokinetics:	SR140333 concentrations were summarized using descriptive statistics [median, arithmetic mean, geometric mean, standard deviation (SD), coefficient of variation, minimum, and maximum].

Summary:

Study population:

A total of 306 patients, including 173 (56.5%) males and 133 (43.5%) females, with a mean age of 43.3 ± 13.5 years (19-79 years), were included in the study. The patients had a mean Clinical Mayo score of 5.6 ± 1.0, and a mean DAI of 7.4 ± 1.1. Overall, patients' demographic and baseline characteristics were well balanced across the 3 groups.

Efficacy:

Clinical remission at Week 8

The overall proportion of patients with clinical remission at Week 8 was not significantly different in the SR140333B 600 mg (21.6%), 1800 mg (23.5%), and placebo (23.5%) groups. No significant differences between groups were observed when considering the intake of steroids at baseline. Additionally, similar results were observed when the constraint of rescue therapy in the clinical remission definition was relaxed.

Main secondary efficacy endpoints

No significant differences were observed between the SR140333B and placebo groups in terms of clinical response at Week 8, endoscopic Mayo score change at endpoint, endoscopic remission at endpoint, or abdominal pain intensity.

Safety:

The percentage of patients having experienced at least one TEAE during the treatment period was similar in the placebo (39.2%) and SR140333B 600 mg/day group (40.2%), and was higher in the SR140333B 1800 mg/day group (52.9%).

No deaths were reported in the study. A total of 9 patients, including 3 patients (2.9%) in each group, experienced serious TEAEs. The incidence of AEs leading to study discontinuation ranged between 2.9% in the placebo group and 5.9% in the SR140333B 1800 mg/group.

In terms of system-organ classes, the most frequently reported TEAEs in the 3 treatment groups were gastrointestinal disorders and nervous system disorders. The distribution of TEAEs was similar in the SR140333B 600 mg/day and placebo groups, except for nausea, which was reported with a higher incidence in the SR140333B 600 mg group (8.8% versus 3.9% in the placebo group). In the SR140333B 1800 mg group, the higher frequency of TEAEs recorded compared to the placebo and SR140333B 600 mg groups was mainly due to gastrointestinal AEs such as nausea, vomiting, and abdominal pain, and to nervous system disorders such as fatigue.

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Safety (continued):	No relevant abnormalities were observed in either treatment group for laboratory parameters, or vital signs. Three cases of asymptomatic prolongation of QTcF interval ≥500 ms occurred in the SR140333B groups (2 in the 600 mg group, and 1 in the 1800 mg group); two cases of QTcF prolongation occurred in patients with normal QTcF interval at baseline; the third one in a patient with prolonged QTcF interval at baseline.
Pharmacokinetics:	Mean (SD) plasma trough concentrations of SR140333 were 617.0 (882.9) pg/mL on Day 7 and 747.4 (537.6) pg/mL on Day 56 for the 600 mg/day dose, and 2590.7 (2706.5) pg/mL on Day 7 and 2207.7 (2001.9) pg/mL on Day 56 for the 1800 mg/day dose. On Day 7, 90 minutes after dosing, mean (SD) plasma concentrations of SR140333 were 6854.4 (6389.3) pg/mL for the 600 mg/day dose, and 14776.1 (11229.6) pg/mL for the 1800 mg/day dose.
Conclusions:	[redacted]

Date of report:	11 September 2007