SYNOPSIS

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Title of the study:	A randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multi-center study evaluating the efficacy and safety of four doses of SR147778 in obese patients (Study DRI5029)
Investigators:	[redacted]
Study centers:	25 active centers located in Europe (France, Finland, Spain), Argentina, and Australia
Publications (reference):	None
Study period: Date first patient enrolled: 26 October 2004 Date last patient completed: 15 November 2005	**Phase of development:** Dose-ranging (Phase 2)
Objectives:	***Primary*** To assess the effect of surinabant on body weight loss over a period of 24 weeks when prescribed with a hypocaloric diet in obese patients. ***Secondary*** • To assess the safety and tolerability of surinabant in obese patients; • to assess the efficacy of surinabant on several secondary parameters (such as waist circumference, metabolic parameters…) when prescribed with a hypocaloric diet in obese patients.
Methodology:	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, four fixed-dose regimens study.
Number of patients Evaluated:	Planned: 300 Randomized: 394 Treated: 394 Efficacy: 394 [modified intent-to-treat (mITT) population]; 316 (completers) Safety: 394 Pharmacokinetics: 203
Diagnosis and main criteria for inclusion:	Males or females, aged 18 to 65 years, with a body mass index (BMI) ≥ 30 and ≤40 kg/m², total cholesterol ≤3 g/L (ie, ≤7.7 mmol/L), triglycerides ≤7 g/L (ie, 7.9 mmol/L), fasting glucose ≤1.6 g/L (ie, 8.9 mmol/L), and hemoglobin A1c (HbA1c) ≤8%.
Investigational product: Doses: Administration: Batch numbers:	surinabant (capsules of 2.5 and 10 mg) 2.5, 5, 10, or 20 mg once daily Oral [redacted]
Duration of treatment: 24 weeks (ie, 6 months)	**Duration of observation:** Between 28 and 36 weeks, including up to 2-week screening, 2 to 3-week placebo run-in, 24-week (± 2 weeks) double-blind treatment, and 4-week (± 1 week) follow-up.

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Reference therapy:	Placebo
Dose:	Not applicable
Administration:	Oral
Batch number(s):	[redacted]
Criteria for evaluation:	
Efficacy:	***Primary endpoint*** Body weight change at 6 months. ***Secondary endpoints*** • Main secondary endpoints: percentages of patients with body weight loss ≥5% and ≥10%, respectively, at 6 months, changes at 6 months in waist circumference, triglycerides, HDL-cholesterol, supine blood pressure (SBP/DBP) and heart rate (HR), fasting blood glucose and HbA1c, percentage of patients with metabolic syndrome at 6 months, percentage of patients with improved, unchanged, or worsened metabolic syndrome at 6 months; • Exploratory secondary endpoints: changes at 6 months in fasting total cholesterol, total/HDL-cholesterol ratio, LDL-cholesterol, LDL/HDL-cholesterol ratio, and fasting insulin; • Other: changes at 6 months in hip circumference, waist/hip ratio, BMI, LDL-particles, apolipoproteins A and B, insulin resistance, beta-cell function, insulin/glucose ratio, leptin, adiponectin, proinflammatory markers (CRP, IL-2, IL-6), patient's satisfaction with the study treatment, food behavior, daily caloric intake and dietary compliance.
Safety:	Safety evaluation included: • reporting and monitoring of adverse events (AEs), • clinical laboratory tests (hematology, serum chemistry, urinalysis), • vital sign measurements [supine and standing HR and blood pressure (BP)], • 12-lead standard electrocardiograms (ECGs), with central review of ECG parameters, • Hospital Anxiety and Depression (HAD) scale (anxiety and depression sub-scores)
Pharmacokinetics:	Determination of plasma trough surinabant concentrations, and assessment of steady-state
Pharmacokinetic/ pharmacodynamic relationship:	Relationship between plasma surinabant concentrations and change in body weight at 6 months.

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Pharmacokinetic sampling times and bioanalytical methods:	***Sampling:*** Plasma samples for surinabant assays was collected in the morning prior to study drug dosing, on Days -1, 28, 84, and 168. Additionally, a plasma sample was collected 28 days after the last dose (Day 196). ***Assay:*** Surinabant plasma concentrations were determined using a validated Liquid Chromatography - Tandem Mass Spectrometry method with a limit of quantification of 5 ng/mL.
Statistical methods:	
Efficacy:	***Primary efficacy analysis*** Body weight loss at 6 months was analyzed using one-way analysis of covariance with a term for treatment and baseline body weight as co-variable for the mITT and completer populations. The last observation carried forward method was used to account for missing or incomplete assessments. ***Secondary efficacy analyses*** All secondary parameters were analyzed on the mITT population using the same approach than the one used for the primary efficacy parameter.
Safety:	The following analyses were performed on the safety population: • all the AEs were coded using Medical Dictionary for Regulatory Activities (8.1 version), and treatment emergent adverse events (TEAEs) were tabulated and summarized by treatment group; • for clinical laboratory parameters, vital signs, and ECG parameters, descriptive statistics were provided, and analyses of potentially clinically significant abnormalities were performed; • for HAD scale, descriptive statistics were provided for the anxiety and depression sub-scores; • relationships between plasma surinabant concentrations and change in QTcB interval and QTcF interval at 6 months.
Pharmacokinetics:	• Trough plasma concentrations of surinabant were summarized by mean, standard deviation (SD), coefficient of variation, minimum and maximum for each dose for drug treated patients at baseline, and Days 28, 84, 168, and 196. • Steady-state was assessed using Helmert approach in the framework of a linear mixed effect model.
Pharmacokinetic/ pharmacodynamic relationship:	The relationship between change in body weight at 6 months and surinabant plasma trough concentrations was analyzed using a linear mixed effect model.

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Summary:

Study population

A total of 505 patients were enrolled in the study, 424 patients entered in the placebo run-in period, and 394 patients (78.0%) were randomized, respectively 83 in the placebo group, 77 in the surinabant 2.5 mg/day group, and 78 in the surinabant 5 mg/day, 10 mg/day and 20 mg/day groups. All randomized patients were exposed to the study drug and 316 patients (80.2%) completed the study treatment period. The majority of randomized patients were females (78.9%). The mean age of the patients was 45.2 years. The mean BMI ranged between 33.7 ± 2.8 kg/m² and 34.5 ± 3.0 kg/m². Most of the patients had normal fasting HDL-cholesterol, triglycerides, glucose, HbA1c, and insulin levels at baseline, and no metabolic syndrome at baseline.

Efficacy results:

Surinabant showed a clear dose-effect on body weight loss ($p<0.0001$). Adjusted mean body weight change ranged from –2.1 kg in the placebo group to –5.2 kg in the surinabant 20 mg group. Pairwise comparisons showed a significant difference in the adjusted mean body weight change between the surinabant 20 mg group and the placebo group (adjusted mean difference= -3.1 kg, $p<0.0001$), and between the surinabant 10 mg group and the placebo group (adjusted mean difference=-1.9 kg, $p = 0.0049$). Surinabant doses of 10 mg and 20 mg also showed statistically significant reductions in BMI, and in waist and hip circumferences in comparison to placebo.

For most of the metabolic parameters (HDL-cholesterol, triglycerides, HbA1c, fasting glucose) and other secondary endpoints, that were generally within normal ranges at baseline, no dose effect or significant effects of surinabant were observed after 6 months of treatment. Adiponectin was significantly increased in the surinabant 10 mg and 20 mg groups. In addition, CRP and cholesterol ratios (total/HDL-C and LDL/HDL-C) were significantly decreased in the surinabant 20 mg group.

Safety results:

The overall clinical safety profile of surinabant was satisfactory in obese patients receiving surinabant 2.5, 5, 10, or 20 mg/day up to 6 months.

Overall, 66.0% of the patients experienced at least 1 TEAE during the study, with similar distribution of TEAEs between the surinabant and placebo groups (61.0%, 61.5%, 66.7%, and 67.9% in the surinabant 2.5, 5, 10, and 20 mg groups versus 72.3% in the placebo group). No death was reported during the study.

A higher incidence of gastrointestinal events, psychiatric disorders, and nervous system disorders was observed in at least 1 surinabant dose group as compared with placebo. The most frequent TEAEs (>5% of patients in any surinabant group, and greater in at least 1 surinabant group than in the placebo group) were diarrhea, nausea, gastroenteritis, insomnia, and dizziness. A dose-effect of surinabant was observed in the incidence of diarrhea and nausea.

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Safety results (*continued*):	The incidence of patients experiencing serious TEAEs was low and comparable across treatment groups. A total of 14 SAEs were reported in 11 patients, including 8 SAEs in 7/311 patients (2.3%) receiving surinabant and 6 SAEs in 4/83 patients (4.8%) in the placebo group. In the surinabant groups, 2 SAEs in 2 patients (mood altered and tonsillectomy) were reported in the 2.5 mg group, 3 SAEs in 2 patients (coronary disease, pregnancy and spontaneous abortion) were reported in the 5 mg group, and 3 SAEs in 3 patients (atrial fibrillation, gastro-oesopheagal reflux disease and partial seizures) were reported in the 20 mg group. In the placebo group, 6 SAEs were reported in 4 patients (ventricular tachycardia, cardiac arrest and anoxic encephalopathy reported in 1 patient, and small intestine leiomyosarcoma, febrile neutropenia, and arthralgia, each in 1 patient). Permanent discontinuation of the study treatment due to TEAEs occurred in 2.6%, 9.0%, 7.7% and 14.1% of patients in the surinabant 2.5 mg, 5 mg, 10 mg and 20 mg groups, respectively, versus 7.2% in the placebo group. The most frequently reported AEs leading to permanent treatment discontinuation in terms of system organ classes (>2% of patients) were psychiatric disorders, nervous system disorders, and gastrointestinal disorders with higher incidence reported in at least 1 surinabant group as compared with placebo. No relevant clinical changes from baseline were observed for clinical laboratory, vital sign, ECG parameters, or HAD scale. No significant correlation was observed between surinabant plasma trough concentrations and QTcB or QTcF intervals.
Pharmacokinetic results:	Steady-state appeared to be reached by Day 84, with the doses of 2.5, 5, 10 and 20 mg/day leading to mean (SD) trough plasma concentrations of 25.3 (18.8) ng/mL, 45.7 (26.2) ng/mL, 90.4 (54.6) ng/mL, and 154.1 (84.0) ng/mL. Body weight change from baseline decreased (reflecting body weight loss) significantly with increase in surinabant steady-state trough concentration ($p<0.0001$).
Conclusions:	[redacted]

Date of report:	08 January 2007