SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, parallel group, fixed-dose, 8-week treatment, multi-center trial evaluating the dose effect relationship for efficacy and the safety of 3 oral doses of surinabant: 2.5, 5 and 10 mg/day as an aid to smoking cessation in cigarette smokers.
Investigators: There was no principal or coordinating Investigator
Study centers: 35 sites from 8 European countries: Belgium, France, Germany, Italy, Norway, Spain, Sweden, Switzerland.
Publications (reference): None
Study period: Date first patient enrolled: 31 January 2007 Date last patient completed: 04 April 2008
Phase of development: 2B
Objectives: ***Primary***: To assess the dose effect relationship of three fixed doses of surinabant on abstinence from smoking in cigarette smokers during the last four weeks of treatment. ***Main secondary*:** To evaluate the dose effect relationship of surinabant on change of body weight. ***Other secondary*:** To evaluate the clinical and biological safety and tolerability of surinabant; to evaluate the dose effect relationship of surinabant on urges for nicotine; and, to measure the plasma trough levels of surinabant.
Methodology: Multicenter, multinational, randomized, double-blind, 4 parallel groups, fixed dose, placebo-controlled study of 14-week duration (8-week treatment segment and 6-week follow-up). The study included 4 consecutive segments, with the Target Quit Date (TQD) planned on D15: *Segment A* (Screening): Drug free period; 1-week pre-inclusion phase from Day-7 to Day-1. Randomization took place at Day-1; *Segment B* (Pre-TQD Period): Treatment period 1; 2-week period from randomization (Day-1) to the day before the TQD (Day 14): patients took their study medication without obligation to stop smoking; Segment C (Post-TQD Period): Treatment period 2; 6-week period from Day 15 (TQD) to Day 56 (Week 8): patients continued taking their study medication while requested to remain abstinent from tobacco use; Segment D (Safety follow-Up): off drug period; 6-week period from Week 8 (end of segment C) to Week 14; 2 safety visits were performed on Week 11 and on Week 14 (ie, 3 and 6 weeks after the last intake of study medication).
Number of patients: Planned: 800 (200 per arm) Randomized: 810 Treated: 807 **Evaluated:** Efficacy: 810 Safety: 807 Pharmacokinetics: 786
Diagnosis and criteria for inclusion: Male and female patients over legal age, smoking at least 10 cigarettes/day as a mean within the 6 months preceding the screening visit.
Investigational product: Surinabant (SR147778); capsules dosed at 2.5, 5, or 10 mg Doses: 2.5 mg/day, or 5 mg/day, or 10 mg/day Administration: oral Batch numbers: 2.5 mg capsules: [redacted]; 5 mg capsules: [redacted]; 10 mg capsules: [redacted]
Duration of treatment: 8 weeks **Duration of observation:** 15 weeks: 1-week screening, 8-week double-blind treatment, and 6-week follow-up.
Reference therapy: Placebo of surinabant; matching capsules Dose: not applicable Administration: oral Batch number: [redacted]

Criteria for evaluation:

Efficacy:

Primary criterion: Continuous abstinence from tobacco smoking at every visit during the last 4 weeks of the treatment period, ie, from Day 29/Week 5 to Day 56/Week 8. Abstinence was defined by concurrence of the following components: the smoking status, obtained through direct inquiry of the patients, using daily recording by the Investigators, indicated abstinence; the exhaled carbon monoxide level, tested as a biomedical marker of smoking status, was ≤10 ppm; and, the plasma cotinine measurements (only assessed at Day 35/Week 5 and Day 56/Week 8), when performed, were ≤8 micrograms/L.

Main secondary criterion: Change in total body weight from baseline to the last evaluation up to and including Week 8.

other secondary criteria: Total score of the Questionnaire of Smoking Urges (QSU), Weekly abstinence rates.

Safety: Surinabant safety was evaluated from Day 1 to Day 98 (Week 1 to Week 14 inclusive) through: adverse events (AEs) reporting, physical examination, clinical laboratory values, vital signs and electrocardiograms.

Pharmacokinetics*:* Plasma trough levels of surinabant were measured at Weeks 2, 5 and 8.

Pharmacokinetic sampling times and bioanalytical methods: sampling times: predose on Visits 4, 7 and 10 (Weeks 2, 5 and 8). Surinabant plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 5 ng/mL.

Statistical methods:

Efficacy:

Populations analyzed: The analyses of efficacy variables were performed on the intent-to-treat (ITT) population, which consisted of all patients who were randomized, irrespective of compliance with the study protocol and procedures. Patients without post-baseline efficacy evaluations were included in the ITT population as treatment failure for the primary endpoint. Patients were analyzed in the treatment group assigned by randomization.

Two other efficacy populations were considered for the purpose of efficacy analyses: the per protocol (PP) population consisted of all ITT patients with no major protocol deviations and was only used for the analysis of the primary and the main secondary endpoints; and, the Completer population consisted of all ITT patients who completed the theoretical treatment period and was only used for the analysis of the primary endpoint, the main secondary endpoint and for the total score of the QSU.

Primary analysis: The primary analysis consisted in a logistic regression with the 4-week continuous abstinence rates from smoking from weeks 5 through 8 as the dependent variable and with no other explanatory variable than the treatment group (surinabant 2.5 mg, 5 mg, 10 mg and placebo), on the ITT population, using a Wald test. The primary goal was to investigate for dose effect relationship, using a linear trend test that was fitted with the dose as continuous covariate. The significance level was 5%. The 4-week continuous abstinence rates for each surinabant dose group and placebo group were provided. In addition, each surinabant dose group was compared with placebo using a Wald test and the odds ratio of each surinabant dose versus placebo and its bilateral 95% confidence interval was computed, using a logistic regression fitted with the dose as class effect.

Main analysis of the key secondary variable: The main analysis of the body weight change from baseline was performed at the last evaluation of theoretical treatment period up to and including W8 on the ITT population, using analysis of covariance (ANCOVA) with factor treatment as fixed effect (4 levels: surinabant 2.5 mg, 5 mg, 10 mg and placebo) and with the centered baseline value as covariate. The dose effect relationship was tested using a linear trend test with the contrast [-7, -3, 1, 9]. The significance level was 5%. In addition, each surinabant dose group was compared with placebo within the framework of ANCOVA. Baseline adjusted LSMEANS by group, as well as LSMEANS difference of each pair-wise comparison of each surinabant dose versus placebo and its 95% confidence interval were provided.

Safety: Spontaneously reported AEs, vital signs, physical findings, electrocardiograms (ECGs), and standard clinical laboratory values were assessed and analyzed on the Treated Population. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened (according to the Investigator advice) or became serious during the on-treatment period, defined as the time from first dose of study medication up to 5 half-lives (42 days) after the last dose of study medication. Other safety information was also analyzed during the on-treatment period.

Pharmacokinetics*:* Plasma concentrations of surinabant were summarized using descriptive statistics [mean, geometric mean, standard deviation (SD), coefficient of variation, minimum, maximum, and median] by visit.

Summary:

Study population: A summary of the analysis populations is provided in [redacted]. Patient disposition, patient demographic and baseline characteristics, and patient smoking history are respectively summarized in [redacted] and [redacted]

Primary efficacy results*:* The study did not show any dose response relationship between placebo (dose 0) and surinabant doses of 2.5-, 5-, or 10-mg/day for the continuous abstinence rates from smoking during the last 4 weeks of treatment (Weeks 5-8). In the ITT population, the regression line slope of the continuous abstinence rate fitted with the dose used as a continuous covariate was -0.02 (95% CI, -0.06 - 0.03; p-value = 0.40). The abstinence rate in the placebo group was 25.2% and numerically lower rates were observed for all surinabant dose groups [redacted]). The pattern of results observed in the completer population was similar to the pattern in the ITT population.

Secondary efficacy results: Results on the body weight change from baseline showed a dose response relationship indicating a decrease in body weight gain in surinabant dose groups, with a slope of the regression line of -7.88 (95% CI, -10.97 to -4.80) ([redacted]). No differences in the QSU total score were observed between the surinabant and placebo groups ([redacted]). No differences in the weekly abstinence rates were observed between the surinabant and placebo groups ([redacted]).

Safety results:

Adverse events:

An overview of the incidence of treatment emergent adverse events (TEAEs), serious TEAEs and adverse events leading to permanent study drug discontinuation is provided in [redacted].

Treatment-emergent adverse events were more frequently reported in the surinabant 10 mg/day group (82.4%) than in the other groups (73.1% in the placebo group, 76.9% in the surinabant 2.5 mg/day group, 74.8% in the surinabant 5 mg/day group). In all treatment groups, TEAEs were mainly reported in the "Psychiatric disorders", "Nervous system disorders", "Gastrointestinal disorders", "Infections and infestations", "General disorders", and "Skin and subcutaneous tissue disorders" primary system-organ classes. The most frequent TEAEs reported in the surinabant groups with an overall greater incidence than in the placebo group but with no dose-relationship, were headache (12.9% to 18.0%), nausea (6.9% to 14.1%), diarrhea (6.0% to 11.2%), anxiety (7.9% to 9.8%), hyperhidrosis (5.5% to 8.4%), and depression (3.5% to 5.9%) [redacted].

Serious treatment-emergent adverse events (TEAEs) were reported with an overall similar incidence in the surinabant groups (12/606 patients; 2.0%) and placebo group (3/201 patients; 1.5%). The highest incidence of serious TEAEs was among patients treated with the lowest dose of surinabant (2.5 mg once daily). No specific pattern was observed for the SAEs reported during the study. No psychiatric or gastrointestinal events were reported as SAEs [redacted].

In the surinabant 2.5 mg/day group, one fatal treatment emergent SAE (cerebral hemorrhage) was reported in a 24 year-old male patient 15 days after the first drug intake.

Overall, 57/606 (9.4%) of patients taking surinabant at any dose discontinued due to a TEAE compared to 16/201 (8.0%) of patients taking placebo. In all treatment groups, the 2 most frequent types of AEs leading to permanent study drug discontinuation were psychiatric disorders (mainly depressed mood/depression, insomnia, anxiety) and gastrointestinal disorders (mainly nausea and diarrhea), with no dose-relationship observed in the surinabant groups [redacted].

Laboratory parameters:

Alanine aminotransferase (ALT) ≥ 3 upper limiy of normal (ULN) and <5 ULN were reported in two patients treated with placebo and in two patients treated with surinabant 2.5 mg/day. Among these 4 patients, 3 had elevated values at baseline. None of the patients with ALT ≥ 3 ULN had total bilirubin potentially clinically significant abnormalities (PCSAs) during the treatment period. Few PCSA values were observed for AST, total bilirubin and gamma-GT in the surinabant treatment groups.

ECG parameters:

Analyses of PCSAs for ECG parameters showed similar results between treatment groups. In the surinabant 5mg/day group, one case of QTcF-interval ≥ 500 ms (524 ms) with an increase ≥ 60 ms (+75 ms) from baseliine was observed at the end of the follow-up period (D98, ie 6 weeks after the end of treatment) in a patient with a normal QTcF-interval at baseline and under treatment (D14 and D56).

Pharmacokinetic results*:*

At visit 10 (Week 8), the mean (SD) plasma trough concentration of surinabant was 22.3 (18.0) ng/mL after repeated doses of 2.5 mg, 41.5 (25.4) ng/mL after repeated doses of 5 mg, and 74.2 (46.4) ng/mL after repeated doses of 10 mg.

Conclusions:

[redacted]

Date of report: 18-Feb-2009

Table 1 – Number (%) of patients included in the analysis populations - Randomized population

	Placebo (N=202)	SR147778		
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)
ITT Population	202 (100%)	199 (100%)	204 (100%)	205 (100%)
Per Protocol population	176 (87.1%)	182 (91.5%)	178 (87.3%)	185 (90.2%)
Completer population	163 (80.7%)	147 (73.9%)	152 (74.5%)	164 (80.0%)
Treated population	201 (99.5%)	199 (100%)	202 (99.0%)	205 (100%)

Note: % calculated using the number of randomized patients as the denominator. For the treated population, patients were analyzed according to the treatment group as treated (i.e. as randomized or as longest exposure in case of unexpected switch) -

Table 2 – Summary of patient disposition - Number (%) - Randomized patients

	Placebo (N=202)	SR147778		
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)
Randomized patients	202 (100%)	199 (100%)	204 (100%)	205 (100%)
Exposed patients	201 (99.5%)	199 (100%)	202 (99.0%)	205 (100%)
Completed study treatment period	163 (80.7%)	147 (73.9%)	152 (74.5%)	164 (80.0%)
Discontinued study treatment period	39 (19.3%)	52 (26.1%)	52 (25.5%)	41 (20.0%)
Reason for treatment discontinuation:				
Lack of efficacy	6 (3.0%)	11 (5.5%)	13 (6.4%)	10 (4.9%)
Adverse event	16 (7.9%)	21 (10.6%)	20 (9.8%)	16 (7.8%)
Poor compliance to protocol	2 (1.0%)	3 (1.5%)	2 (1.0%)	4 (2.0%)
Subject's request	9 (4.5%)	9 (4.5%)	12 (5.9%)	5 (2.4%)
Subject lost to follow-up	4 (2.0%)	3 (1.5%)	2 (1.0%)	3 (1.5%)
Other reason	2 (1.0%)	5 (2.5%)	3 (1.5%)	3 (1.5%)
Completed the whole study	168 (83.2%)	163 (81.9%)	170 (83.3%)	178 (86.8%)
Discontinued study	34 (16.8%)	36 (18.1%)	34 (16.7%)	27 (13.2%)
Reason for follow-up discontinuation:				
Adverse event	3 (1.5%)	3 (1.5%)	4 (2.0%)	2 (1.0%)
Poor compliance to protocol	1 (0.5%)	4 (2.0%)	4 (2.0%)	5 (2.4%)
Subject's request	15 (7.4%)	17 (8.5%)	19 (9.3%)	10 (4.9%)
Subject lost to follow-up	8 (4.0%)	3 (1.5%)	4 (2.0%)	6 (2.9%)
Other reason	6 (3.0%)	8 (4.0%)	3 (1.5%)	4 (2.0%)
Lack of efficacy	1 (0.5%)	0	0	0
Death	0	1 (0.5%)	0	0

Note: % calculated using the number of randomized patients as the denominator.

Table 3 – Summary of demographic and patient characteristics at baseline - ITT population

	Placebo (N=202)	SR147778			
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)	All (N=810)
Gender, [n(%)]					
Number	202	199	204	205	810
Male	75 (37.1%)	83 (41.7%)	95 (46.6%)	83 (40.5%)	336 (41.5%)
Female	127 (62.9%)	116 (58.3%)	109 (53.4%)	122 (59.5%)	474 (58.5%)
Race, [n(%)]					
Number	202	199	204	205	810
Black	1 (0.5%)	0	1 (0.5%)	0	2 (0.2%)
Caucasian	199 (98.5%)	197 (99.0%)	200 (98.0%)	204 (99.5%)	800 (98.8%)
Asian, Oriental	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (0.4%)
Other	2 (1.0%)	1 (0.5%)	2 (1.0%)	0	5 (0.6%)
Age (years)					
Number	202	199	204	205	810
Mean (SD)	44.8 (10.5)	44.3 (10.8)	45.0 (11.1)	45.7 (10.3)	45.0 (10.7)
Median	45.5	44.0	44.0	46.0	45.0
Min : Max	18 : 71	20 : 69	21 : 76	20 : 73	18 : 76
Age group, [n(%)]					
Number	202	199	204	205	810
[18 - 44]	96 (47.5%)	101 (50.8%)	103 (50.5%)	89 (43.4%)	389 (48.0%)
[45 - 64]	101 (50.0%)	93 (46.7%)	93 (45.6%)	111 (54.1%)	398 (49.1%)
>=65	5 (2.5%)	5 (2.5%)	8 (3.9%)	5 (2.4%)	23 (2.8%)
BMI (kg/m^2)					
Number	202	199	204	205	810
Mean (SD)	25.30 (4.57)	25.38 (5.37)	25.48 (4.02)	26.07 (4.56)	25.56 (4.65)
Median	24.87	24.22	24.95	25.42	24.90
Min : Max	17.0 : 39.9	17.0 : 60.4	18.6 : 41.4	17.6 : 43.9	17.0 : 60.4

Note: Number corresponds to the count of patients with non missing data used for the calculation

Table 4 – Summary of smoking history - ITT population

	Placebo (N=202)	SR147778			
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)	All (N=810)
Time since regular smoking years					
Number	202	199	204	205	810
Mean (SD)	27.0 (10.6)	27.0 (10.5)	28.1 (11.4)	28.4 (10.0)	27.6 (10.6)
Median	28.0	27.0	27.0	29.0	28.0
Min : Max	2 : 58	5 : 52	4 : 60	4 : 50	2 : 60
Number of cigarettes/day					
Number	202	199	204	205	810
Mean (SD)	21.6 (9.1)	21.4 (8.5)	22.3 (9.1)	21.7 (8.2)	21.7 (8.7)
Median	20.0	20.0	20.0	20.0	20.0
Min : Max	7 : 60	10 : 60	10 : 60	10 : 50	7 : 60
Number of previous quit attempts					
Number	201	198	204	205	808
Mean (SD)	2.6 (2.5)	2.5 (2.4)	2.9 (3.8)	3.5 (7.6)	2.9 (4.6)
Median	2.0	2.0	2.0	2.0	2.0
Min : Max	0 : 13	0 : 15	0 : 40	0 : 100	0 : 100
Attempts to quit smoking in the past three months [n(%)]					
Number	178	177	177	176	708
Yes	1 (0.6%)	3 (1.7%)	5 (2.8%)	3 (1.7%)	12 (1.7%)
Longest previous abstinent period [n(%)]					
< 24h / never	28 (13.9%)	22 (11.1%)	29 (14.2%)	29 (14.1%)	108 (13.3%)
1 day - < 1 month	51 (25.2%)	50 (25.1%)	53 (26.0%)	38 (18.5%)	192 (23.7%)
1 month - < 1 year	74 (36.6%)	76 (38.2%)	78 (38.2%)	94 (45.9%)	322 (39.8%)
>= 1 year	49 (24.3%)	51 (25.6%)	44 (21.6%)	44 (21.5%)	188 (23.2%)
Difficulties during previous attempts [n(%)]					
Permanent state of something missing	51 (29.0%)	51 (28.8%)	49 (27.7%)	46 (26.1%)	197 (27.9%)
Not to smoke at special moments when taste well	63 (35.8%)	62 (35.0%)	68 (38.4%)	68 (38.6%)	261 (37.0%)
Both equally difficult	62 (35.2%)	64 (36.2%)	60 (33.9%)	62 (35.2%)	248 (35.1%)

	Placebo (N=202)	SR147778			
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)	All (N=810)
Motivation scale					
Number	202	199	204	205	810
Mean (SD)	8.5 (1.2)	8.6 (1.2)	8.5 (1.2)	8.5 (1.2)	8.6 (1.2)
Median	8.5	9.0	9.0	8.0	9.0
Min : Max	6 : 10	6 : 10	6 : 10	6 : 10	6 : 10
Fagerstrom total score					
Number	201	196	201	205	803
Mean (SD)	5.5 (2.2)	5.5 (2.2)	5.7 (2.2)	5.5 (2.1)	5.6 (2.2)
Median	5.0	5.0	6.0	6.0	6.0
Min : Max	0 : 10	0 : 10	0 : 10	0 : 10	0 : 10
Fagerstrom total score [n(%)]					
<7	138 (68.7%)	130 (66.3%)	123 (61.2%)	140 (68.3%)	531 (66.1%)
>=7	63 (31.3%)	66 (33.7%)	78 (38.8%)	65 (31.7%)	272 (33.9%)
Borelli scale total score					
Number	202	199	201	205	807
Mean (SD)	32.3 (14.3)	30.5 (15.0)	31.8 (13.6)	31.4 (13.4)	31.5 (14.1)
Median	32.0	29.0	32.0	30.0	31.0
Min : Max	6 : 60	6 : 60	6 : 60	6 : 60	6 : 60

Note: Number corresponds to the count of patients with non missing data used for the calculation

Table 5 – Summary of 4-week continuous abstinence rates week 5-Week 8 - ITT population

	Placebo (N=202)	SR147778		
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)
Abstinent	51 (25.2%)	45 (22.6%)	45 (22.1%)	44 (21.5%)
Wald P-value vs Placebo		0.9374	0.7659	0.5927
Odds ratios vs Placebo		0.865	0.838	0.809
95% CI		(0.55 to 1.37)	(0.53 to 1.33)	(0.51 to 1.28)
Trend test				
Estimate (SE)	-0.02 (0.02)			
95% CI	(-0.06 to 0.03)			
P-value	0.3999			

Note: p-value come from Wald's test following logistic regression

Table 6 – Summary of body weight - Last evaluation up to and including Week 8 - ITT population

	Placebo (N=202)	SR147778		
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)
Baseline				
Number	193	194	198	202
Mean (SD)	72.5 (15.0)	73.6 (16.8)	73.4 (14.3)	74.9 (15.7)
Median	70.5	71.0	73.0	73.5
Min : Max	45 : 116	44 : 142	48 : 124	44 : 128
Change from baseline at endpoint				
Number	193	194	198	202
LS Mean (SE)	1.19 (0.13)	0.75 (0.13)	0.53 (0.13)	0.24 (0.13)
LS Mean difference (SE)		-0.44 (0.19)	-0.66 (0.19)	-0.95 (0.19)
95% CI		(-0.81 to -0.07)	(-1.03 to -0.29)	(-1.32 to -0.58)
P-value vs Placebo		0.0210	0.0004880	0.0000006
Trend test				
Estimate (SE)	-7.88 (1.57)			
95% CI	(-10.97 to -4.80)			
P-value	0.0000007			

Note: Number as statistics parameter refers to number of patients with baseline and post-baseline up to W8 values
P-value vs Placebo comes from Student's t-test of comparisons of ANCOVA baseline adjusted LSMEANS
Linear trend test applied using the contrast [-7, -3, 1, 9]

Table 7 – Summary of QSU-brief scale total score - Last evaluation up to and including Week 8 - ITT population

	Placebo (N=202)	SR147778		
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)
Baseline				
Number	188	190	198	201
Mean (SD)	29.9 (21.0)	31.5 (19.4)	33.3 (19.5)	29.3 (19.3)
Median	23.5	25.0	28.0	24.0
Min : Max	10 : 100	10 : 98	10 : 100	10 : 100
Change from baseline at endpoint				
Number	188	190	198	201
LS Mean (SE)	-9.15 (1.17)	-9.53 (1.17)	-9.42 (1.15)	-7.40 (1.14)
LS Mean difference (SE)		-0.37 (1.66)	-0.27 (1.64)	1.75 (1.63)
95% CI		(-3.63 to 2.88)	(-3.49 to 2.95)	(-1.45 to 4.95)
P-value vs Placebo		0.8210	0.8696	0.2841
Trend test				
Estimate (SE)	16.60 (13.62)			
95% CI	(-10.13 to 43.33)			
P-value	0.2231			

Note: Number as statistics parameter refers to number of patients with baseline and post-baseline up to W8 values
P-value comes from Student's t-test of comparisons of ANCOVA baseline adjusted LSMEANS

Table 8 – Summary of weekly abstinence rates by visit - ITT population

	Placebo (N=202)	SR147778		
		2,5 mg (N=199)	5 mg (N=204)	10 mg (N=205)
Day 7				
N(%)	1 (0.5%)	0	1 (0.5%)	2 (1.0%)
P-value vs Placebo		1.0000	1.0000	1.0000
Day 14				
N(%)	7 (3.5%)	2 (1.0%)	12 (5.9%)	3 (1.5%)
P-value vs Placebo		0.1749	0.2489	0.1921
Day 21				
N(%)	31 (15.3%)	22 (11.1%)	31 (15.2%)	28 (13.7%)
P-value vs Placebo		0.2046	0.9664	0.6287
Day 28				
N(%)	68 (33.7%)	62 (31.2%)	72 (35.3%)	76 (37.1%)
P-value vs Placebo		0.5917	0.7296	0.4719
Day 35				
N(%)	62 (30.7%)	52 (26.1%)	63 (30.9%)	58 (28.3%)
P-value vs Placebo		0.3112	0.9670	0.5954
Day 42				
N(%)	72 (35.6%)	62 (31.2%)	68 (33.3%)	69 (33.7%)
P-value vs Placebo		0.3408	0.6244	0.6739
Day 49				
N(%)	70 (34.7%)	66 (33.2%)	71 (34.8%)	70 (34.1%)
P-value vs Placebo		0.7531	0.9746	0.9142
Day 56				
N(%)	56 (27.7%)	55 (27.6%)	54 (26.5%)	58 (28.3%)
P-value vs Placebo		0.9849	0.7765	0.8981

Note: P-value comes from chi-square test if the expected number of observations is at least 5, otherwise it comes from Fisher's exact test

Table 9 – Overview of SR147778 safety profile: number (%) of patients - Treated population

	Placebo (N=201)	SR147778		
		2,5 mg (N=199)	5 mg (N=202)	10 mg (N=205)
Patients with any TEAE (including SAEs)	147 (73.1%)	153 (76.9%)	151 (74.8%)	169 (82.4%)
Patients with any serious TEAE (inluding SAEs leading to death)	3 (1.5%)	6 (3.0%)	4 (2.0%)	2 (1.0%)
Patients with any TEAE leading to death	0	1 (0.5%)	0	0
Any Death	0	1 (0.5%)	0	0
Patients permanently discontinuing treatment due to TEAE	16 (8.0%)	21 (10.6%)	20 (9.9%)	16 (7.8%)

Note: TEAE: Treatment emergent adverse event
SAE: Serious adverse event
Any death as regards on treatment and post-treatment periods
Adverse events coded in MedDRA Version 10.1.1

Table 10 - Number (%) of patients experiencing TEAE(s) at a frequency ≥1%, presented by primary system organ class and preferred term - Treated population

Primary system organ class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Any Class	147 (73.1%)	153 (76.9%)	151 (74.8%)	169 (82.4%)
Psychiatric disorders	76 (37.8%)	72 (36.2%)	67 (33.2%)	82 (40.0%)
Depressed mood	25 (12.4%)	24 (12.1%)	20 (9.9%)	25 (12.2%)
Insomnia	23 (11.4%)	26 (13.1%)	19 (9.4%)	23 (11.2%)
Anxiety	15 (7.5%)	16 (8.0%)	16 (7.9%)	20 (9.8%)
Initial insomnia	9 (4.5%)	5 (2.5%)	7 (3.5%)	13 (6.3%)
Depression	8 (4.0%)	7 (3.5%)	10 (5.0%)	12 (5.9%)
Early morning awakening	7 (3.5%)	5 (2.5%)	9 (4.5%)	7 (3.4%)
Middle insomnia	5 (2.5%)	5 (2.5%)	7 (3.5%)	7 (3.4%)
Sleep disorder	4 (2.0%)	3 (1.5%)	7 (3.5%)	4 (2.0%)
Nervousness	2 (1.0%)	3 (1.5%)	2 (1.0%)	4 (2.0%)
Stress	1 (0.5%)	2 (1.0%)	3 (1.5%)	3 (1.5%)
Apathy	3 (1.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Decreased interest	3 (1.5%)	4 (2.0%)	3 (1.5%)	0
Feeling of despair	2 (1.0%)	2 (1.0%)	1 (0.5%)	0
Nervous system disorders	63 (31.3%)	68 (34.2%)	63 (31.2%)	75 (36.6%)
Headache	27 (13.4%)	31 (15.6%)	26 (12.9%)	37 (18.0%)
Dizziness	29 (14.4%)	25 (12.6%)	20 (9.9%)	27 (13.2%)
Somnolence	5 (2.5%)	3 (1.5%)	5 (2.5%)	6 (2.9%)
Paraesthesia	3 (1.5%)	7 (3.5%)	10 (5.0%)	5 (2.4%)
Disturbance in attention	2 (1.0%)	2 (1.0%)	5 (2.5%)	5 (2.4%)
Dysgeusia	1 (0.5%)	3 (1.5%)	2 (1.0%)	4 (2.0%)
Hypoaesthesia	4 (2.0%)	1 (0.5%)	0	3 (1.5%)
Gastrointestinal disorders	62 (30.8%)	54 (27.1%)	61 (30.2%)	74 (36.1%)
Nausea	11 (5.5%)	22 (11.1%)	14 (6.9%)	29 (14.1%)
Diarrhoea	17 (8.5%)	12 (6.0%)	20 (9.9%)	23 (11.2%)
Dyspepsia	5 (2.5%)	4 (2.0%)	7 (3.5%)	9 (4.4%)
Vomiting	6 (3.0%)	7 (3.5%)	3 (1.5%)	5 (2.4%)
Dry mouth	2 (1.0%)	4 (2.0%)	5 (2.5%)	4 (2.0%)
Toothache	3 (1.5%)	1 (0.5%)	3 (1.5%)	4 (2.0%)
Abdominal pain upper	8 (4.0%)	11 (5.5%)	8 (4.0%)	3 (1.5%)
Frequent bowel movements	1 (0.5%)	0	2 (1.0%)	3 (1.5%)
Abdominal pain	4 (2.0%)	2 (1.0%)	1 (0.5%)	3 (1.5%)

Primary system organ class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Flatulence	8 (4.0%)	1 (0.5%)	7 (3.5%)	2 (1.0%)
Constipation	7 (3.5%)	4 (2.0%)	1 (0.5%)	2 (1.0%)
Stomach discomfort	0	0	3 (1.5%)	1 (0.5%)
Gastritis	3 (1.5%)	2 (1.0%)	2 (1.0%)	0
Infections and infestations	40 (19.9%)	46 (23.1%)	44 (21.8%)	43 (21.0%)
Nasopharyngitis	17 (8.5%)	19 (9.5%)	17 (8.4%)	17 (8.3%)
Influenza	5 (2.5%)	8 (4.0%)	11 (5.4%)	7 (3.4%)
Gastroenteritis	3 (1.5%)	3 (1.5%)	5 (2.5%)	6 (2.9%)
Bronchitis	1 (0.5%)	3 (1.5%)	3 (1.5%)	3 (1.5%)
Rhinitis	0	1 (0.5%)	2 (1.0%)	3 (1.5%)
Pharyngitis	2 (1.0%)	0	1 (0.5%)	3 (1.5%)
Upper respiratory tract infection	4 (2.0%)	5 (2.5%)	4 (2.0%)	2 (1.0%)
Cystitis	1 (0.5%)	2 (1.0%)	0	2 (1.0%)
Urinary tract infection	0	0	4 (2.0%)	1 (0.5%)
Sinusitis	4 (2.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)
Tooth abscess	1 (0.5%)	2 (1.0%)	0	1 (0.5%)
Post procedural infection	0	2 (1.0%)	0	0
General disorders and administration site conditions	25 (12.4%)	28 (14.1%)	36 (17.8%)	30 (14.6%)
Asthenia	15 (7.5%)	11 (5.5%)	14 (6.9%)	11 (5.4%)
Irritability	4 (2.0%)	2 (1.0%)	12 (5.9%)	8 (3.9%)
Fatigue	5 (2.5%)	7 (3.5%)	7 (3.5%)	6 (2.9%)
Influenza like illness	2 (1.0%)	2 (1.0%)	2 (1.0%)	1 (0.5%)
Chest pain	0	2 (1.0%)	1 (0.5%)	1 (0.5%)
Skin and subcutaneous tissue disorders	10 (5.0%)	14 (7.0%)	26 (12.9%)	23 (11.2%)
Hyperhidrosis	6 (3.0%)	11 (5.5%)	17 (8.4%)	16 (7.8%)
Pruritus	1 (0.5%)	1 (0.5%)	1 (0.5%)	5 (2.4%)
Erythema	0	0	3 (1.5%)	0
Respiratory, thoracic and mediastinal disorders	9 (4.5%)	9 (4.5%)	10 (5.0%)	13 (6.3%)
Pharyngolaryngeal pain	0	5 (2.5%)	2 (1.0%)	2 (1.0%)
Cough	3 (1.5%)	2 (1.0%)	1 (0.5%)	2 (1.0%)

Primary system organ class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Injury, poisoning and procedural complications	7 (3.5%)	11 (5.5%)	9 (4.5%)	13 (6.3%)
Accidental overdose	0	4 (2.0%)	0	4 (2.0%)
Procedural pain	0	2 (1.0%)	2 (1.0%)	1 (0.5%)
Fall	1 (0.5%)	2 (1.0%)	2 (1.0%)	0
Musculoskeletal and connective tissue disorders	17 (8.5%)	21 (10.6%)	18 (8.9%)	11 (5.4%)
Back pain	3 (1.5%)	8 (4.0%)	4 (2.0%)	5 (2.4%)
Neck pain	1 (0.5%)	0	0	3 (1.5%)
Arthralgia	3 (1.5%)	0	3 (1.5%)	0
Pain in extremity	3 (1.5%)	0	2 (1.0%)	0
Osteoarthritis	0	2 (1.0%)	1 (0.5%)	0
Myalgia	2 (1.0%)	2 (1.0%)	0	0
Ear and labyrinth disorders	1 (0.5%)	2 (1.0%)	4 (2.0%)	6 (2.9%)
Vertigo	1 (0.5%)	0	1 (0.5%)	4 (2.0%)
Investigations	4 (2.0%)	0	4 (2.0%)	6 (2.9%)
Heart rate increased	0	0	2 (1.0%)	4 (2.0%)
Blood creatine phosphokinase increased	3 (1.5%)	0	1 (0.5%)	1 (0.5%)
Eye disorders	2 (1.0%)	2 (1.0%)	6 (3.0%)	5 (2.4%)
Vision blurred	0	1 (0.5%)	3 (1.5%)	1 (0.5%)
Cardiac disorders	3 (1.5%)	3 (1.5%)	3 (1.5%)	5 (2.4%)
Palpitations	1 (0.5%)	2 (1.0%)	2 (1.0%)	3 (1.5%)
Vascular disorders	4 (2.0%)	8 (4.0%)	6 (3.0%)	4 (2.0%)
Hot flush	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)
Hypertension	1 (0.5%)	3 (1.5%)	2 (1.0%)	1 (0.5%)
Metabolism and nutrition disorders	2 (1.0%)	4 (2.0%)	6 (3.0%)	4 (2.0%)
Increased appetite	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)
Anorexia	0	2 (1.0%)	1 (0.5%)	2 (1.0%)
Decreased appetite	0	2 (1.0%)	3 (1.5%)	0

Primary system organ class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Reproductive system and breast disorders	6 (3.0%)	4 (2.0%)	5 (2.5%)	3 (1.5%)
Erectile dysfunction	1 (0.5%)	3 (1.5%)	1 (0.5%)	0
Renal and urinary disorders	0	2 (1.0%)	2 (1.0%)	1 (0.5%)
Pollakiuria	0	2 (1.0%)	0	0

Only rows with frequency of at least 1 % in at least one column are shown
Note: Primary SOC and preferred term sorted as in the "All TEAEs" table
Adverse events coded in MedDRA Version 10.1.1

Table 11 - Number (%) of patients experiencing serious TEAE(s), presented by primary system organ class and preferred term - Treated population

Primary system organ class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Any Class	3 (1.5%)	6 (3.0%)	4 (2.0%)	2 (1.0%)
Nervous system disorders	0	1 (0.5%)	1 (0.5%)	0
Dizziness	0	0	1 (0.5%)	0
Cerebral haemorrhage	0	1 (0.5%)	0	0
Infections and infestations	1 (0.5%)	2 (1.0%)	0	0
Post procedural infection	0	1 (0.5%)	0	0
Pneumonia	1 (0.5%)	1 (0.5%)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.5%)	0
Pulmonary embolism	0	0	1 (0.5%)	0
Injury, poisoning and procedural complications	2 (1.0%)	0	2 (1.0%)	0
Fall	1 (0.5%)	0	1 (0.5%)	0
Tendon rupture	1 (0.5%)	0	1 (0.5%)	0
Ankle fracture	1 (0.5%)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (0.5%)
Bursitis	0	0	0	1 (0.5%)
Cardiac disorders	0	1 (0.5%)	0	0
Myocardial infarction	0	1 (0.5%)	0	0
Reproductive system and breast disorders	0	0	0	1 (0.5%)
Uterine haemorrhage	0	0	0	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (1.0%)	0	0
Breast cancer	0	1 (0.5%)	0	0
Prostate cancer	0	1 (0.5%)	0	0
Immune system disorders	0	1 (0.5%)	0	0
Anaphylactic shock	0	1 (0.5%)	0	0
Hepatobiliary disorders	0	0	1 (0.5%)	0
Cholelithiasis	0	0	1 (0.5%)	0

Note: Primary SOC and preferred term sorted as in the "All TEAEs" table
Adverse events coded in MedDRA Version 10.1.1

Table 12 – Summary of patients experiencing TEAE(s), leading to study drug discontinuation, presented by primary system organ class and preferred term - Treated population

Primary system oragn class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Any Class	16 (8.0%)	21 (10.6%)	20 (9.9%)	16 (7.8%)
Psychiatric disorders	7 (3.5%)	7 (3.5%)	5 (2.5%)	4 (2.0%)
Depressed mood	4 (2.0%)	3 (1.5%)	0	1 (0.5%)
Insomnia	0	2 (1.0%)	0	2 (1.0%)
Anxiety	0	1 (0.5%)	1 (0.5%)	1 (0.5%)
Depression	2 (1.0%)	2 (1.0%)	2 (1.0%)	0
Middle insomnia	1 (0.5%)	0	1 (0.5%)	0
Nervousness	0	0	0	1 (0.5%)
Stress	0	0	0	1 (0.5%)
Decreased interest	0	1 (0.5%)	0	0
Feeling of despair	0	1 (0.5%)	0	0
Loss of libido	0	1 (0.5%)	1 (0.5%)	0
Nervous system disorders	2 (1.0%)	4 (2.0%)	4 (2.0%)	3 (1.5%)
Headache	0	1 (0.5%)	1 (0.5%)	0
Dizziness	2 (1.0%)	1 (0.5%)	2 (1.0%)	0
Paraesthesia	1 (0.5%)	0	1 (0.5%)	0
Disturbance in attention	0	0	0	1 (0.5%)
Hypoaesthesia	0	1 (0.5%)	0	1 (0.5%)
Migraine	0	0	0	1 (0.5%)
Cerebral haemorrhage	0	1 (0.5%)	0	0
Gastrointestinal disorders	2 (1.0%)	9 (4.5%)	3 (1.5%)	7 (3.4%)
Nausea	0	5 (2.5%)	1 (0.5%)	2 (1.0%)
Diarrhoea	1 (0.5%)	2 (1.0%)	0	3 (1.5%)
Dyspepsia	0	1 (0.5%)	0	1 (0.5%)
Vomiting	0	2 (1.0%)	1 (0.5%)	0
Abdominal pain upper	1 (0.5%)	2 (1.0%)	0	0
Frequent bowel movements	0	0	0	1 (0.5%)
Stomach discomfort	0	0	0	1 (0.5%)
Gastritis	0	0	1 (0.5%)	0
Infections and infestations	1 (0.5%)	0	0	0
Pneumonia	1 (0.5%)	0	0	0

Primary system oragn class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
General disorders and administration site conditions	2 (1.0%)	2 (1.0%)	1 (0.5%)	3 (1.5%)
Asthenia	2 (1.0%)	0	0	2 (1.0%)
Irritability	0	0	0	1 (0.5%)
Fatigue	0	1 (0.5%)	0	0
Pain	0	0	1 (0.5%)	0
Malaise	0	1 (0.5%)	0	0
Skin and subcutaneous tissue disorders	2 (1.0%)	1 (0.5%)	0	2 (1.0%)
Hyperhidrosis	2 (1.0%)	0	0	0
Pruritus	0	1 (0.5%)	0	2 (1.0%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.5%)	0	0
Dyspnoea	0	1 (0.5%)	0	0
Injury, poisoning and procedural complications	0	1 (0.5%)	2 (1.0%)	0
Fall	0	0	1 (0.5%)	0
Tendon rupture	0	0	1 (0.5%)	0
Limb injury	0	1 (0.5%)	0	0
Ear and labyrinth disorders	1 (0.5%)	0	0	0
Vertigo	1 (0.5%)	0	0	0
Investigations	2 (1.0%)	0	1 (0.5%)	0
Blood creatine phosphokinase increased	2 (1.0%)	0	1 (0.5%)	0
Eye disorders	1 (0.5%)	0	2 (1.0%)	0
Dry eye	0	0	1 (0.5%)	0
Visual acuity reduced	0	0	1 (0.5%)	0
Scotoma	1 (0.5%)	0	0	0
Cardiac disorders	0	0	0	1 (0.5%)
Palpitations	0	0	0	1 (0.5%)
Vascular disorders	0	0	1 (0.5%)	0
Hypertension	0	0	1 (0.5%)	0

Primary system oragn class / Preferred Term	Placebo (N=201)	SR147778 2,5 mg (N=199)	SR147778 5 mg (N=202)	SR147778 10 mg (N=205)
Metabolism and nutrition disorders	0	0	1 (0.5%)	1 (0.5%)
Anorexia	0	0	1 (0.5%)	1 (0.5%)
Reproductive system and breast disorders	0	1 (0.5%)	1 (0.5%)	0
Erectile dysfunction	0	1 (0.5%)	1 (0.5%)	0
Renal and urinary disorders	0	0	1 (0.5%)	0
Renal pain	0	0	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.5%)	0
Breast cancer in situ	0	0	1 (0.5%)	0
Immune system disorders	0	1 (0.5%)	0	0
Anaphylactic shock	0	1 (0.5%)	0	0
Pregnancy, puerperium and perinatal conditions	0	1 (0.5%)	0	0
Pregnancy	0	1 (0.5%)	0	0
Social circumstances	1 (0.5%)	0	0	0
Verbal abuse	1 (0.5%)	0	0	0

Note: Primary SOC and preferred term sorted as in the "All TEAEs" table
Adverse events coded in MedDRA Version 10.1.1