SYNOPSIS

Title of the study: An international, seven-week, double-blind, placebo-controlled, two parallel group study to assess the efficacy of dianicline 40 mg bid as an aid to smoking cessation in cigarette smokers (EFC5515)

Investigator(s): Multiple sites

Study center(s): France, Spain, Belgium, and Scandanavia

Publications (reference): Not applicable

Study period:
Date first patient enrolled: 14-Jun-2006
Date last patient completed: 05-Jun-2007

Phase of development: 3

Objectives:
The primary objective of this study was to demonstrate the efficacy of dianicline 40 mg bid versus placebo as an aid to smoking cessation in cigarette smokers after seven weeks of treatment.

The secondary objectives were:
- to demonstrate the efficacy of dianicline on craving.
- to evaluate the clinical and biological safety and tolerability of dianicline during a 7-week treatment period.
- to evaluate the abstinence rate during a 19-week follow-up post treatment period.

Methodology: Seven-week multicenter, multinational, randomized, placebo-controlled, double-blind, 2-parallel-group, fixed dose study in Europe

Number of patients: Planned: 600 patients (300 patients per treatment group)
Randomized: 302 placebo; 300 dianicline
Treated: 302 placebo; 300 dianicline
Efficacy: 302 placebo; 300 dianicline
Safety: 302 placebo; 300 dianicline
Pharmacokinetics: 218

Diagnosis and criteria for inclusion: Outpatients over legal age, smoking at least 10 cigarettes/day as a mean within the 2 months preceding the screening visit.

Investigational product: Dianicline (SSR591813L)
Dose: 40 mg capsule bid
Administration: Oral
Batch number(s): [redacted]

Duration of treatment: 7 weeks
Duration of observation: 27 weeks

Reference therapy: Placebo
Dose: 40 mg capsule bid
Administration: Oral
Batch number(s): [redacted]

Criteria for evaluation: The current report is a synopsis report, and as such, only the primary and main secondary efficacy results as well as the main safety data are presented here. All individual data can be found in the appendices.
The primary efficacy variable was the 4-week continuous abstinence rate; ie, the percentage of patients counted as abstinent during the last 4 weeks of the treatment period.

For safety, the following criteria were evaluated for the treated population and analyzed using descriptive statistics: spontaneously reported adverse events (AEs), vital signs, physical findings, electrocardiograms (ECGs), and standard clinical laboratory values during the on-treatment period, defined as the time from first dose of study medication up to 1 day after the last dose of study medication.

Statistical methods: The analyses of efficacy variables were performed on the intent-to-treat (ITT) population. The ITT population 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. The Per Protocol (PP) population consisted of all ITT patients who completed the theoretical treatment period and was only used for the analysis of the primary and the key secondary endpoints.

The primary analysis consisted in a logistic regression with the 4-week continuous abstinence rates from smoking from Weeks 4 through 7 as the dependent variable and with no other explanatory variable than the treatment group (dianicline 40 mg and placebo), on the ITT population. The 4 week continuous abstinence rates of the two groups were compared using a Wald test. The significance level was 5%. The bilateral 95% confidence interval of the odds ratio was computed.

The main analysis of the key secondary variable was performed at the last evaluation up to and including Week 7 on the ITT population, using an analysis of covariance (ANCOVA) with factor treatment (two levels: dianicline and placebo) as fixed effect and with the centered baseline value as covariate. The adjusted means (SAS LSMEANS) were computed and the comparisons versus placebo were performed using a Student's test. The centered baseline for each patient was her/his baseline value minus the mean of the baseline based on the whole population.

For the analyses of the primary endpoint, no adjustments for multiple comparisons were needed as only one com;parison of dianicline 40 mg bid treatment group versus placebo was planned.

To handle the multiplicity issue for the key secondary endpoint, a step down procedure was used: only if the primary variable was significant at 5% level, would the main secondary endpoint be analyzed, using a 5% significance level.

Summary:

No switch of treatment occurred during the study treatment period. Treatment was discontinued by 25.2% of the patients in the placebo group and 23.0% of patients in the dianicline group (**Table 1**); the most common reason for treatment discontinuation was subject request (8.9% in the placebo group) and AE (7.7%) in the dianicline group. The treatment dropout rates were consistent with the dropout rates observed in literature in studies using the same population and the same short term design. A complete listing of patient disposition is provided in the CSR Appendix.

Table 1 – Summary of patient disposition number (%) – randomized patients

	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Randomized patients	302 (100%)	300 (100%)
Exposed patients	302 (100%)	300 (100%)
Completed study treatment period	226 (74.8%)	231 (77.0%)
Discontinued study treatment period	76 (25.2%)	69 (23.0%)
Reason for treatment discontinuation		
Lack of efficacy	19 (6.3%)	11 (3.7%)
Adverse event	13 (4.3%)	23 (7.7%)
Poor compliance to protocol	7 (2.3%)	5 (1.7%)
Subject's request	27 (8.9%)	20 (6.7%)
Subject lost to follow-up	9 (3.0%)	7 (2.3%)
Other reason	1 (0.3%)	3 (1.0%)

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

Summary (continued):
Overall, demographic characteristics of the ITT population were similar between the SSR591813L and placebo groups; the median age was 45 years; the majority of patients were Caucasians (**Table 2**).

Table 2 – Summary of demographic and patient characteristics at baseline - ITT population

	Placebo (N=302)	SSR591813L 40 mg bid (N=300)	All (N=602)
Gender, [n (%)]			
Number	302	300	602
Male	141 (46.7%)	127 (42.3%)	268 (44.5%)
Female	161 (53.3%)	173 (57.7%)	334 (55.5%)
Race, [n (%)]			
Number	302	300	602
Black	2 (0.7%)	2 (0.7%)	4 (0.7%)
Caucasian	296 (98.0%)	298 (99.3%)	594 (98.7%)
Asian, Oriental	1 (0.3%)	0 (0.0%)	1 (0.2%)
Other	3 (1.0%)	0 (0.0%)	3 (0.5%)
Age (years)			
Number	302	300	602
Mean (SD)	45.3 (9.9)	45.0 (10.6)	45.1 (10.2)
Median	45.0	45.0	45.0
Min : Max	21 : 65	22 : 71	21 : 71
Age group, [n(%)]			
Number	302	300	602
[18 - 44]	136 (45.0%)	145 (48.3%)	281 (46.7%)
[45 - 64]	163 (54.0%)	145 (48.3%)	308 (51.2%)
≥65	3 (1.0%)	10 (3.3%)	13 (2.2%)
BMI (kg/m^2)			
Number	302	300	602
Mean (SD)	25.90 (4.59)	25.54 (4.31)	25.72 (4.45)
Median	25.04	25.09	25.08
Min : Max	17.7 : 49.1	16.8 : 55.1	16.8 : 55.1

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

Summary (continued):
The treatment groups were well matched in terms of smoking patterns (**Table 3**).

Table 3 – Summary of smoking history (ITT population)

	Placebo (N=302)	SSR591813L 40 mg bid (N=300)	All (N=602)
Time since regular smoking years			
Number	302	300	602
Mean (SD)	28.0 (9.9)	28.3 (10.8)	28.2 (10.3)
Median	30.0	29.0	30.0
Min : Max	2 : 50	5 : 54	2 : 54
Number of cigarettes/day			
Number	302	300	602
Mean (SD)	21.4 (8.4)	20.8 (7.2)	21.1 (7.8)
Median	20.0	20.0	20.0
Min : Max	10 : 70	10 : 50	10 : 70
Number of previous quit attempts			
Number	302	300	602
Mean (SD)	3.5 (4.6)	3.3 (4.5)	3.4 (4.6)
Median	2.0	2.0	2.0
Min : Max	0 : 50	0 : 50	0 : 50
Attempts to quit smoking in the past three months [n(%)]			
Number	280	261	541
Yes	8 (2.9%)	2 (0.8%)	10 (1.8%)
Longest previous abstinent period [n(%)]			
<24h / never	26 (8.6%)	43 (14.3%)	69 (11.5%)
1 day - <1 month	61 (20.2%)	62 (20.7%)	123 (20.4%)
1 month - <1 year	141 (46.7%)	123 (41.0%)	264 (43.9%)
≥1 year	74 (24.5%)	72 (24.0%)	146 (24.3%)
Difficulties during previous attempts [n(%)]			
Permanent state of something missing	85 (31.1%)	80 (31.7%)	165 (31.4%)
Not to smoke at special moments when taste well	77 (28.2%)	91 (36.1%)	168 (32.0%)
Both equally difficult	111 (40.7%)	81 (32.1%)	192 (36.6%)
Motivation scale			
Number	302	300	602
Mean (SD)	8.6 (1.2)	8.6 (1.1)	8.6 (1.1)
Median	9.0	9.0	9.0
Min : Max	6 : 10	6 : 10	6 : 10
Fagerstrom total score			
Number	301	297	598
Mean (SD)	5.6 (2.1)	5.9 (1.9)	5.7 (2.0)
Median	6.0	6.0	6.0
Min : Max	0 : 10	1 : 10	0 : 10
Fagerstrom total score [n(%)]			
<7	194 (64.5%)	182 (61.3%)	376 (62.9%)
≥7	107 (35.5%)	115 (38.7%)	222 (37.1%)

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

Primary efficacy results:
No significant difference was detected on the continuous abstinence rates in the SSR 591813L group compared to placebo during the last 4 weeks of treatment in the ITT (**Table 4**) and PP (completed treatment patients; **Table 5**) populations.

Summary (continued):
Primary efficacy results (continued):

Table 4 – 4-week continuous abstinence W4 - W7 (ITT population)

	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Abstinent	62 (20.5%)	72 (24.0%)
p-value		0.307
Odds ratios vs Placebo		1.22
95% CI		(0.83 to 1.80)

Note: p-value comes from Wald test

Table 5 – 4-week continuous abstinence W4 - W7 - PP population

	Placebo (N=226)	SSR591813L 40 mg bid (N=231)
Abstinent	61 (27.0%)	69 (29.9%)
p-value		0.495
Odds ratios vs Placebo		1.15
95% CI		(0.77 to 1.73)

Note: p-value comes from Wald test

Main secondary efficacy results:
Results observed in the ITT population with SSR591813L 40 bid showed a reduction in total craving as assessed by the QSU brief scale compared to the p-value in the table is given for descriptive purpose (**Table 6**).

Table 6 – Questionnaire on Smoking Urges brief form (QSU) total score- last evaluation up to and including W7 (ITT population)

QSU Brief total score	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Baseline		
Number	290	287
Mean (SD)	35.4 (19.8)	36.0 (20.4)
Median	31.0	32.0
Min : Max	10 : 100	10 : 100
Change from baseline at endpoint		
Number	290	287
LS Mean (SE)	-11.23 (0.99)	-14.59 (1.00)
LS Mean Difference (SE)		-3.35 (1.41)
95% CI		(-6.12 to -0.59)
p-value vs Placebo		0.0175

Note: Number as statistics parameter refers to number of patients with baseline and post-baseline up to W7 values
p-value comes from Student's t-test of comparisons of ANCOVA baseline adjusted LSMEANS

Safety results:
Overall, treatment emergent adverse events (TEAEs) were frequently reported during the study and in slightly higher number of patients in the dianicline group than in the placebo group (**Table 7**). The incidence of serious adverse events (SAEs) was low, and similar between treatment groups, and a higher number of patients in the dianicline group discontinued treatment due to AEs, compared with the placebo group (13 [4.3%] discontinuations in the placebo arm compared to 23 (7.7%) in the dianicline arm (**Table 10**). The most common AE in the dianicline (2.3%) and placebo (1.0%) arms was nausea. The most common TEAE leading to discontinuation was nausea (2.3% in the dianicline arm and 0.3% in the placebo arm). In the placebo arm, there were 3 cardiac events (2 ECG abnormal QT interval and 1 ECG QT prolongation).

Summary (continued):
Safety results (continued):

Table 7 – Overview of dianicline safety profile (treated population)

	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Patients with any TEAE (including SAEs)	185 (61.3%)	207 (69.0%)
Patients with any serious TEAE (including SAEs leading to death)	3 (1.0%)	3 (1.0%)
Patients with any TEAE leading to death	0 (0.0%)	0 (0.0%)
Any Death	0 (0.0%)	0 (0.0%)
Patients permanently discontinuing treatment due to TEAE	13 (4.3%)	23 (7.7%)

Note: Any death as regards on treatment and post-treatment periods
Adverse events coded in MedDRA Version 10

A summary of the number (%) of patients who experienced at least 1 TEAE that occurred with an incidence of ≥1% in any treatment group is presented in **Table 8**, ordered by decreasing frequency within the system organ class (SOC) in the SSR591813L group. The most frequently reported SOCs (≥10% in any group) reported in SSR591813L group were gastrointestinal disorders; nervous system disorders; infections and infestations and psychiatric disorders. These were reported more frequently in the SSR591813L 40 mg bid group than in placebo group except for the SOC infections and infestations. The most common reported AE with SSR591813L was nausea, which occurred in 76 (25.3%) patients. Seven patients in the SSR591813L group (2.3%) discontinued study drug due to nausea (see **Table 10**).

Table 8 – Summary of all TEAEs presented by primary system organ class and preferred term at a frequency ≥1% - treated population

Primary system organ class / Preferred Term	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Any Class	185 (61.3%)	207 (69.0%)
Gastrointestinal disorders	70 (23.2%)	123 (41.0%)
Nausea	27 (8.9%)	76 (25.3%)
Diarrhoea	11 (3.6%)	28 (9.3%)
Vomiting	8 (2.6%)	12 (4.0%)
Flatulence	9 (3.0%)	10 (3.3%)
Abdominal pain upper	6 (2.0%)	9 (3.0%)
Dyspepsia	5 (1.7%)	9 (3.0%)
Abdominal pain	6 (2.0%)	7 (2.3%)
Constipation	5 (1.7%)	6 (2.0%)
Dry mouth	7 (2.3%)	4 (1.3%)
Gastrooesophageal reflux disease	0 (0.0)	3 (1.0%)
Nervous system disorders	53 (17.5%)	64 (21.3%)
Headache	36 (11.9%)	44 (14.7%)
Dizziness	8 (2.6%)	13 (4.3%)
Disturbance in attention	6 (2.0%)	4 (1.3%)
Migraine	3 (1.0%)	3 (1.0%)
Infections and infestations	58 (19.2%)	45 (15.0%)
Nasopharyngitis	21 (7.0%)	11 (3.7%)
Influenza	6 (2.0%)	10 (3.3%)
Bronchitis	4 (1.3%)	4 (1.3%)
Gastroenteritis	5 (1.7%)	4 (1.3%)
Upper respiratory tract infection	4 (1.3%)	4 (1.3%)
Sinusitis	3 (1.0%)	3 (1.0%)
Psychiatric disorders	39 (12.9%)	44 (14.7%)
Insomnia	19 (6.3%)	11 (3.7%)
Depression	1 (0.3%)	8 (2.7%)
Depressed mood	6 (2.0%)	7 (2.3%)
Sleep disorder	2 (0.7%)	6 (2.0%)
Nervousness	3 (1.0%)	4 (1.3%)
General disorders and administration site conditions	13 (4.3%)	19 (6.3%)

(continued)

Summary (continued):
Safety results (continued):

Primary system organ class / Preferred Term	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Fatigue	1 (0.3%)	11 (3.7%)
Asthenia	2 (0.7%)	3 (1.0%)
Musculoskeletal and connective tissue disorders	14 (4.6%)	19 (6.3%)
Arthralgia	1 (0.3%)	5 (1.7%)
Back pain	3 (1.0%)	5 (1.7%)
Myalgia	5 (1.7%)	3 (1.0%)
Investigations	15 (5.0%)	13 (4.3%)
Creatinine renal clearance decreased	2 (0.7%)	5 (1.7%)
Respiratory, thoracic and mediastinal disorders	16 (5.3%)	11 (3.7%)
Pharyngolaryngeal pain	7 (2.3%)	3 (1.0%)
Throat irritation	3 (1.0%)	3 (1.0%)
Skin and subcutaneous tissue disorders	19 (6.3%)	9 (3.0%)
Pruritus	3 (1.0%)	6 (2.0%)
Hyperhidrosis	6 (2.0%)	2 (0.7%)
Rash	5 (1.7%)	2 (0.7%)
Ear and labyrinth disorders	7 (2.3%)	3 (1.0%)
Vertigo	5 (1.7%)	3 (1.0%)

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

The incidence of SAEs was low and similar in both treatment groups. A summary of on-treatment SAEs is provided in **Table 9**.

Table 9 – Summary of treatment emergent serious adverse events presented by primary system organ class and preferred term – on-treatment period (TEAEs) – treated population

Primary system organ class / Preferred Term	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Any Class	3 (1.0%)	3 (1.0%)
Gastrointestinal disorders	1 (0.3%)	0 (0.0%)
Subileus	1 (0.3%)	0 (0.0%)
Infections and infestations	0 (0.0%)	1 (0.3%)
Appendicitis	0 (0.0%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (0.3%)
Asthma	0 (0.0%)	1 (0.3%)
Vascular disorders	1 (0.3%)	0 (0.0%)
Thrombophlebitis	1 (0.3%)	0 (0.0%)
Cardiac disorders	1 (0.3%)	1 (0.3%)
Angina pectoris	0 (0.0%)	1 (0.3%)
Supraventricular tachycardia	1 (0.3%)	0 (0.0%)

Note: Primary SOC and preferred term sorted as in the "All TEAEs" table
Adverse events coded in MedDRA Version 10

Summary (continued):

Safety results (continued):

Slightly more patients in the SSR591813L group had TEAEs that led to discontinuation of treatment compared with placebo; the SOCs most frequently reported were gastrointestinal disorders and nervous system disorders (**Table 10**).

Table 10 – Summary of TEAEs leading to treatment discontinuation presented by primary system organ class and preferred term – on-treatment period (TEAEs) – treated population

Primary system organ class / Preferred Term	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
Any Class	13 (4.3%)	23 (7.7%)
Gastrointestinal disorders	3 (1.0%)	13 (4.3%)
Nausea	1 (0.3%)	7 (2.3%)
Diarrhoea	0	4 (1.3%)
Vomiting	0	4 (1.3%)
Abdominal pain upper	1 (0.3%)	2 (0.7%)
Abdominal pain	1 (0.3%)	1 (0.3%)
Nervous system disorders	0	5 (1.7%)
Headache	0	2 (0.7%)
Dizziness	0	1 (0.3%)
Somnolence	0	1 (0.3%)
Syncope vasovagal	0	1 (0.3%)
Infections and infestations	1 (0.3%)	0 (0.0%)
Pneumonia	1 (0.3%)	0 (0.0%)
Psychiatric disorders	3 (1.0%)	3 (1.0%)
Insomnia	2 (0.7%)	1 (0.3%)
Depression	0 (0.0%)	1 (0.3%)
Stress	1 (0.3%)	1 (0.3%)
General disorders and administration site conditions	0 (0.0%)	1 (0.3%)
Fatigue	0 (0.0%)	1 (0.3%)
Investigations	3 (1.0%)	4 (1.3%)
Creatinine renal clearance decreased	0 (0.0%)	1 (0.3%)
Blood creatine phosphokinase increased	0 (0.0%)	1 (0.3%)
Hepatic enzyme increased	0 (0.0%)	1 (0.3%)
Aspartate aminotransferase increased	0 (0.0%)	1 (0.3%)
Electrocardiogram pr prolongation	0 (0.0%)	1 (0.3%)
Electrocardiogram qt interval abnormal	2 (0.7%)	0 (0.0%)
Electrocardiogram qt prolonged	1 (0.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders	2 (0.7%)	1 (0.3%)
Pruritus	0 (0.0%)	1 (0.3%)
Rash generalised	1 (0.3%)	0 (0.0%)
Urticaria papular	1 (0.3%)	0 (0.0%)
Injury, poisoning and procedural complications	1 (0.3%)	0 (0.0%)
Rib fracture	1 (0.3%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	1 (0.3%)
Arrhythmia supraventricular	0 (0.0%)	1 (0.3%)
Ear and labyrinth disorders	0 (0.0%)	1 (0.3%)
Vertigo	0 (0.0%)	1 (0.3%)
Immune system disorders	0 (0.0%)	1 (0.3%)
Hypersensitivity	0 (0.0%)	1 (0.3%)
Renal and urinary disorders	1 (0.3%)	0 (0.0%)
Haematuria	1 (0.3%)	0 (0.0%)

Note: Primary SOC and preferred term sorted as in the "All TEAEs" table
Adverse events coded in MedDRA Version 10

Summary (continued):

Safety results (continued):

There were no deaths during the study treatment period. One fatal SAE was recorded during the screening period: a 50 years-old Caucasian female, had a cerebral hemorrhage 3 days after her screening visit. This patient was hospitalized and died 2 days later. Complete listings of TEAEs, deaths and other SAEs, AEs leading to treatment discontinuation, and a listing of all AEs are provided in the CSR Appendix.

Potentially clinically significant abnormalities (PCSAs) in liver enzymes were reported during the study in slightly higher number of patients in the dianicline group than in the placebo group. ALT PCSAs ≥3 were reported in 2 patients of the dianicline group during the 7 weeks of treatment but no increase of total bilirubin was observed in these 2 patients (**Table 11**).

Table 11 – Liver function - summary of patients with at least one on-treatment potentially clinically significant abnormality – treated population

Laboratory criteria PCSA criteria Baseline status [n/N(%)]	Placebo (N=302)	SSR591813L 40 mg bid (N=300)
AST (SGOT-ASAT)		
>2.0 ULN		
Total	2/270 (0.7%)	4/272 (1.5%)
Abnormal high	0/3 (0.0%)	1/8 (12.5%)
Normal/missing	2/267 (0.7%)	3/264 (1.1%)
ALT (SGPT-ALAT)		
>2.0 ULN		
Total	3/270 (1.1%)	7/272 (2.6%)
Abnormal high	2/14 (14.3%)	1/11 (9.1%)
Normal/missing	1/256 (0.4%)	6/261 (2.3%)
Total bilirubin		
≥1.5 ULN		
Total	0/267 (0.0%)	2/271 (0.7%)
Abnormal high	0/1 (0.0%)	2/9 (22.2%)
Normal/missing	0/266 (0.0%)	0/262 (0.0%)
Alkaline phosphatase		
≥1.5 ULN		
Total	0/271 (0.0%)	2/272 (0.7%)
Abnormal high	0/3 (0.0%)	0/5 (0.0%)
Normal/missing	0/268 (0.0%)	2/267 (0.7%)
Gamma GT		
≥3 ULN		
Total	2/273 (0.7%)	5/272 (1.8%)
Abnormal high	2/21 (9.5%)	3/21 (14.3%)
Normal/missing	0/252 (0.0%)	2/251 (0.8%)

Note: ULN = Upper limit of normal
% calculated using the number of patients with at least one event (n) over the number of patients assessed (N)
Baseline status is defined according to laboratory range or PCSA status
Baseline values within laboratory limits or below LLN are grouped in Normal/Missing

Conclusion:

[redacted]

Date of report: 05-Aug-2008