2. SYNOPSIS

Name of Sponsor/Company: Evotec Neurosciences GmbH	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
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TITLE OF STUDY: A Phase 2 Multicentre, Randomised, Double-Blind, Parallel Group, Placebo-Controlled, Study to Evaluate the Effectiveness of EVT 302 in Smoking Cessation, Effect on its Own and in Combination with Open Label Nicotine Replacement.

INVESTIGATOR(S) AND STUDY SITE(S):

A total of 9 investigative sites screened subjects in the study. All study sites were located in [redacted]

STUDY DATES: From: 22 Aug 2008 To: 06 Mar 2009

PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

Primary Study Objective

- To evaluate the efficacy and safety of EVT 302 compared with placebo as an aid to smoking cessation in chronic cigarette smokers.

Secondary Study Objectives

- To assess the efficacy of EVT 302 when combined with Nicotine Replacement Therapy (NRT).
- To assess the efficacy of EVT 302 compared with placebo in reducing the symptoms of nicotine withdrawal.

METHODOLOGY:

This was a multicentre, randomised, double-blind, parallel group, placebo controlled study of the safety and efficacy of EVT 302 alone and in combination with NRT, as an aid to smoking cessation in chronic cigarette smokers. Following initial screening subjects entered an 8-week treatment period. Subjects were randomly assigned to four treatment groups, and received either EVT 302 5 mg, or placebo, or open label NRT (21 mg patch) plus placebo, or NRT plus EVT 302 5 mg. All medications were taken once daily (o.d.). EVT 302 or placebo treatment started on Day 1, 7 days before a predefined target quit date (TQD; Day 8) and continued for 7 weeks after the TQD. NRT started on the TQD and continued for 7 weeks after the TQD. After completion of the treatment period, subjects returned 4 weeks later for follow-up evaluations. A total of 11 visits were planned, including one safety follow-up.

At Visit 1 subjects were issued with an electronic diary to record the number of cigarettes smoked each day, beginning and ending at midnight. At Visit 2 (baseline) the TQD was selected, this being 7 days after the start of treatment, and subjects received an educational booklet on smoking cessation and up to 10 minutes of brief, individualised support and advice by an experienced staff member to assist smoking cessation. Throughout the study smoking status was assessed and carbon monoxide (CO) measurements were used to validate reported abstinence. All subjects who completed the treatment period were followed for an additional 4 weeks (follow-up period).

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NUMBER OF SUBJECTS:

At least 400 subjects were planned to be recruited in the study (140 in the EVT 302 5 mg group, 140 in the placebo group, 60 in the NRT plus placebo group, and 60 in the NRT plus EVT 302 5 mg group).

The actual number of subjects screened, randomised and who completed the study are as follows:

Total screened: 739

Total randomised: 414

Total completed: 375

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male or female subjects, 18 to 70 years of age, who were chronic smokers but motivated to quit smoking, who smoked at least 10 cigarettes per day, and with at least one unsuccessful attempt to quit smoking in the last 2 years but with no more than 1 month of continued abstinence in the last 12 months were screened.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:

- EVT 302 5 mg tablet o.d taken in the morning together with 200 mL of still water. Batch numbers: 0120D and 0187D (expiry date: Jun 2010).

DURATION OF TREATMENT: 8 weeks

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:

- Placebo tablet to match EVT 302 o.d. taken in the morning together with 200 mL of still water. Batch numbers: 0119D and 0186D (expiry date: Apr 2013).
- NRT 21 mg patch (NiQuitin® containing 21 mg of nicotine) o.d. administered locally in a transparent matrix TTS. Batch numbers: 080617/V (expiry date: Aug 2009).

CRITERIA FOR EVALUATION:

Primary Efficacy Variable:

The primary endpoint for this study was the 4-week Continuous Quit Rate (CQR) for the last 4 weeks of treatment (Week 5 to 8). Subjects were classified as responders if they reported complete abstinence from cigarette smoking and other nicotine use (except for nicotine replacement where allocated to NRT) for the last 4 weeks of treatment confirmed with exhaled CO measurements (<10 ppm). Subjects who withdrew prior to completing Week 8 were classed as non-responders. Subjects who withdrew prior to starting Week 5 were excluded from the analysis.

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Secondary Efficacy Variables:

- Number and percentage of subjects who achieved a 7-week abstinence after quit date from 1 week after start of treatment to Week 8.
- Number and percentage of subjects who achieve a 7-day abstinence in each week of the study between Weeks 2 and 8.
- Summary of the average number of cigarettes smoked per day in each week of the study and over the entire course of the study (Weeks 2-8).
- Summary of the change from baseline in the average daily number of cigarettes smoked in each week and over the entire course of the study (Weeks 2-8).
- Time to the quitting smoking, defined as the number of days from the TQD to the last cigarette smoked in the study (subjects had to have completed at least one further week with no cigarettes smoked).
- Summary of each of the questionnaires examining nicotine withdrawal symptoms and the reinforcing effects of smoking assessed. Summaries contained the actual scores and the changes in baseline at each study week.
    - Minnesota Nicotine Withdrawal Scale (MNWS) questionnaire.
    - Brief Questionnaire of Smoking Urges (QSU-brief).
    - Modified Cigarette Evaluation Questionnaire (mCEQ).
- Summary of the answers to the question: “would you take this type of treatment again as an aid to smoking cessation?”
- Summary of CO readings in each week of the study.
- Summary of cotinine measurements for the EVT 302 alone and placebo alone treatment groups.

Safety:

Safety was assessed using incidence of treatment-emergent adverse events (TEAEs), Electrocardiogram (ECG) monitoring, physical examinations (including neurological examinations), ophthalmology assessments (including slit lamp examinations), haematology, biochemistry, urinalysis and vital signs and weight.

STATISTICAL METHODS:

For all statistical analyses described, only the difference between EVT 302 without NRT and placebo without NRT groups was formally tested. An additional secondary treatment comparison was made between EVT 302 and placebo, each in the presence of NRT. For this secondary treatment comparison, 95% confidence intervals (CIs) of the treatment difference estimates were calculated and in the event that such CIs indicated significance (i.e. did not contain zero), a descriptive p-value was also reported.

For the analysis of the primary efficacy outcome, the null hypothesis (proportion of responders in the EVT 302 alone group equal to proportion of responders in the placebo alone group) was tested using a Chi-squared or Fisher’s exact test in the Intent to Treat (ITT) population. P-values for treatment difference were calculated together with 95% CIs for the estimates of treatment difference. A supportive analysis using the Per Protocol (PP) population was also produced in the same manner.

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STATISTICAL METHODS (Cont.):

Further supportive analyses were performed which looked at alternative methods of classifying subjects who withdrew from the study between Weeks 5 and 8. A confirmatory analysis on the proportion of responders was performed using a logistic regression with treatment group as a factor. Potential prognostic factors reported during the screening period were also examined. Where modeling was performed, centre was included as a random effect. Any other covariates to be included in the model were included as fixed effects.

The proportion of responders for 7-week quit rates was analysed using a Chi-squared or Fisher's exact test in the same manner as the primary analysis variable. The change from baseline in the average cigarettes smoked per day at each week were analysed using a one-way repeated measures analysis of variance (ANOVA) model. In addition, the change from baseline in the overall average cigarettes smoked per day in Weeks 2-8 was analysed in a one-ay ANOVA model. Kaplan-Meier (KM) estimates were used to estimate the proportion of subjects who had not yet quit smoking.

Summary statistics by treatment group and visit were produced for all other efficacy and all safety parameters, together with changes from baseline if applicable. TEAEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and were tabulated by preferred term and system organ class (SOC), by both severity and relationship to study drug.

SUMMARY OF RESULTS AND CONCLUSIONS:

Efficacy:

Primary Efficacy Results:

For the 4-week CQR between Weeks 5-8, the percentage of responders was 18.8% and 16.1% for the EVT 302 and placebo alone treatment groups, respectively. The percentage was higher in the NRT treatment groups, with responder rates of 33.3% and 30.4% for EVT 302 and placebo in the presence of NRT, respectively. The difference of around 3% favourable to EVT 302, both with or without NRT, was neither clinically nor statistically significant. These results were corroborated in the PP population, as well as in the supportive analyses performed by two alternative methods for classifying subjects who withdrew before Week 8.

Although differences were not statistically significant, subjects on EVT 302 were found to have a greater chance of quitting smoking than those in the placebo group (odds ratios for the comparison between EVT 302 and placebo, alone or in the presence of NRT, of 1.23 and 1.20, respectively). By adjusting for the prognostic factors found to have a significant effect on the CQR, the second confirmatory logistic regression model showed similar results, with a slightly increased and slightly decreased odds ratio of 1.45 and 1.13 for the treatment comparisons between EVT 302 and placebo alone and between EVT 302 with NRT and placebo with NRT, respectively. Subjects with higher Fagerström total scores at baseline, family members who smoked, more previous attempts to quit smoking and with a higher average daily cigarette intake at baseline were less likely to quit smoking (odds ratios being 0.69, 0.46, 0.63 and 0.63, respectively). Older subjects and males were more likely to quit smoking (odds ratio of 1.35 and 1.82, respectively).

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SUMMARY OF RESULTS AND CONCLUSIONS (Cont.):

Primary Efficacy Results (cont.):

Subgroup analyses performed on each prognostic factor showed a similar trend with a percentage of responders generally higher in the NRT groups. Sample sizes were too small to allow for any statistically significant treatment differences.

Secondary Efficacy Results:

For the 7-week CQR between Weeks 2-8, no significant differences were found between EVT 302 and placebo, with a percentage of responders of 4.9% for both EVT 302 and placebo alone treatment groups, and 11.5% and 10.0% for EVT 302 and placebo each in the presence of NRT, respectively. A similar trend was observed for the abstinence rates by study week, with no meaningful differences found between EVT 302 and placebo in general and with slightly higher rates of responders in the NRT treatment groups.

All treatment groups showed a substantial and sustained decrease from baseline in the average number of cigarettes smoked per day with generally little difference observed between EVT 302 and placebo. Throughout the study, this was about 13-14 cigarettes in the non-NRT groups and about 16-17 cigarettes in the NRT groups. The results from the one-way ANOVA model corroborated this and showed a slightly greater but non-significant decrease from baseline to Weeks 2-8 for placebo compared to EVT 302 both alone and in the presence of NRT, with a treatment difference estimate of 0.92 (CI: -0.80, 2.63) and 0.74 (CI: -1.84, 3.31), respectively.

For those subjects who quit smoking, mean time to last cigarette smoked was similar among the four groups, ranging from 7.9 to 9.5 days across all treatment groups. In all treatment groups 75% of those subjects who quit did so within 12-15 days of the TQD. Estimated statistics taken from KM analysis including all subjects and censoring subjects who did not quit smoking showed a mean time to last cigarette smoked ranging from 25.1 to 33.1 days across all treatment groups. The large amount of censored data and the relatively small sample sizes made it difficult to draw any conclusions about differences or lack of differences among the treatment groups.

The results in the Completers population of all secondary efficacy variables corroborated those seen in the ITT population.

There was little change from baseline in mean MNWS scores across all groups, which were generally around 1-2 (slight to mild withdrawal symptoms) at baseline, increased to mild to moderate symptoms at the Week 2 visit and progressively decreased again to a value similar to that at baseline, with very small changes from baseline to Week 8/ET. All treatment groups experienced a marked progressive improvement in smoking urges symptoms throughout the study with a decrease in mean QSU-Brief total scores from baseline to Week 8/ET of about 250-300 across all groups. A decrease/improvement from baseline to Week 8/ET was also generally observed in mean mCEQ questionnaire scores. Although a generally greater improvement/decrease of mean scores was observed in the NRT groups, no notable differences were found between EVT 302 and placebo. The majority of the subjects who smoked during the week prior to end of study (63 77% across all groups) had a $\geq$3 point decrease in smoking satisfaction.

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SUMMARY OF RESULTS AND CONCLUSIONS (Cont.):

Secondary Efficacy Results (Cont):

Approximately 80-90% of the subjects in all treatment groups were willing to take the treatment again as an aid to smoking cessation. Major reasons given were little or no side effects, ease of use and few or no withdrawal symptoms. In approximately 50% of the subjects in the NRT groups and 27% in the EVT 302 and placebo alone treatment groups the reason given to be willing to take the treatment again was that the treatment helped them to successfully quit smoking. Of the approximately 10-20% of subjects in all treatment groups who were reluctant to take the treatment again as an aid to smoking cessation, the majority of them stated that the treatment was unsuccessful at helping them to quit smoking. Very few subjects (less than 2%) gave side effects, significant withdrawal symptoms and easy to use as reasons for being unwilling to take the treatment again.

The percentage of subjects with CO measurements ≥10 ppm decreased during the study from more than 90% in all treatment groups at baseline to approximately 40% in the EVT 302 and placebo alone groups, 19.7% in the EVT 302 with NRT treatment group and 27.9% in the placebo with NRT treatment group at end of study. Cotinine measurements in the EVT 302 alone and placebo alone treatment groups also decreased during the study with no meaningful differences observed between the groups.

Safety:

The administration of EVT 302 5 mg tablets alone for 8 weeks was generally safe and well tolerated in subjects participating in this study.

Overall, the incidence of subjects experiencing a TEAE during the study was comparable between the EVT 302 and placebo alone treatment groups (78.6% and 77.2%, respectively). The addition of NRT patches to EVT 302 dosing slightly increased the incidence of TEAEs (85.2% and 80.3% in the EVT 302 with NRT and placebo with NRT groups, respectively).

Most TEAEs were moderate (48.5%) or mild (25.7%). Few subjects had TEAEs that were severe (5.1%). The distribution of TEAEs by severity was comparable among the four treatment groups, although slightly higher in the EVT 302 with NRT treatment group (8.2% vs 3-5% in the other three groups).

By SOC, the majority of the TEAEs were related to infections and infestations; nervous system disorders and gastrointestinal disorders. By preferred term, the most common TEAE was nasopharyngitis, whose incidence was comparable between the EVT 302 alone (30.3%), placebo alone (33.1%) and EVT 302 with NRT (34.4%) treatment groups and slightly lower in the placebo with NRT (24.6%) treatment group. The other TEAEs that were reported by ≥5% of the subjects in any treatment group were respiratory tract infection, rhinitis, dizziness, headache, constipation, diarrhoea, flatulence, nausea, sleep disorder, application site pruritus, cough and hyperhidrosis. Of these TEAEs, a higher incidence (by ≥5%) was observed in the EVT 302 alone group compared with the placebo alone group for rhinitis (8.3% versus 1.4%). However, viral infections and rhinitis can be frequently found in study populations as being related to seasonal factors and this apparent difference can be considered to be coincidental in nature.

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SUMMARY OF RESULTS AND CONCLUSIONS (Cont.):

Safety (Cont.):

Overall, approximately a third of the subjects experienced at least one drug-related TEAE in the EVT 302 and placebo alone treatment groups and the placebo with NRT treatment group. The addition of NRT patches to EVT 302 dosing increased the incidence of TEAEs that were considered drug related to approximately half of the subjects. By SOC, the majority of drug-related TEAEs were related to nervous system disorders (14.8%), gastrointestinal disorders (11.9%), psychiatric disorders (9.2%) and general disorders and administration site conditions (8.3%). The EVT 302 and placebo alone treatment groups had a similar incidence of drug-related TEAEs except for those related to psychiatric disorders, which appeared to occur more frequently in the EVT 302 alone group (10.3% versus 5.5%) and those related to nervous system disorders, which appeared to occur more frequently in the placebo alone group (15.9% versus 11.0%). However, by preferred term no relevant differences were found between both groups for the most common events observed (in ≥2% of the subjects) under psychiatric disorders (insomnia and sleep disorders) and nervous system disorders (dizziness and headache).

In the NRT groups, EVT 302 appeared to have a higher incidence compared to placebo of TEAEs related to nervous system disorders (21.3% vs 14.8%), gastrointestinal disorders (21.3% vs 16.4%) and general disorders and administration site conditions (21.3% vs 11.5%). The following events tended to ocurr more frequently (≥5%) in the EVT 302 with NRT group compared to the placebo with NRT group: dizziness (8.2% vs 1.6%), diarrhoea (8.2% vs 1.6%), application site pruritus (6.6% vs 1.6%), and hyperhidrosis (6.6% vs 1.6%). However, all these differences were not observed in the absence of NRT (between EVT 302 and placebo) and may be considered to be coincidental.

The addition of NRT to EVT 302 tended to increase (≥5%) the incidence of TEAEs that were related to study medication for nervous system disorders (11.0% to 21.3%), gastrointestinal disorders (9.7% to 21.3%), general disorders and administration site conditions (4.1% to 21.3%) and skin and subcutaneous tissue disorders (2.1% to 8.2%). By preferred term, dizziness, diarrhoea, application site pruritus and hyperhidrosis were more frequently observed with the EVT 302 NRT combined treatment compared to the other three treatment groups.

The incidence of drug-related abnormal liver function tests (LFTs) and cardiovascular irregularities was generally low (<5%) in all treatment groups, with no apparent increase when comparing either EVT 302 or placebo alone with the NRT treatment groups. No individual changes of concern in LFTs were found.

A low number of subjects permanently discontinued study treatment due to a TEAE. A total of six subjects permanently discontinued treatment with EVT 302/placebo due to a TEAE; of these, three subjects were in the EVT 302 alone treatment group, two were in the placebo alone treatment group and one subject was in the EVT 302 with NRT treatment group. TEAEs leading to EVT 302/placebo discontinuation were considered related to the study medication in one subject in the EVT 302 alone group and in one subject in the placebo alone group. In the NRT groups, eight subjects in the EVT 302 with NRT group and six subjects in the placebo with NRT group permanently discontinued NRT patches due to a TEAE. TEAEs leading to NRT patches withdrawal were considered to be related to study treatment in all subjects except in one subject in the placebo with NRT group.

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SUMMARY OF RESULTS AND CONCLUSIONS (Cont.):

Safety (Cont.):

Four subjects experienced an SAE during the study. Of these, three subjects were in the EVT 302 alone treatment group and one subject was in the EVT 302 with NRT treatment group. All four SAEs were unlikely to be related or were unrelated to study medication and resolved. No subjects died during the study.

There were no clinically relevant findings or notable clinical differences among the treatment groups with regards to laboratory analyses, vital signs, ECG, physical examination, neurological, ophthalmological assessments and other assessments (inclusion and exclusion criteria violation, pregnancy test results, and smoking support and advice and telephone contacts). In particular, there was no suggestion of any hypertensive reactions occurring in this population (no restriction of diet tyramine content).

SUMMARY OF RESULTS AND CONCLUSIONS (Cont.):

CONCLUSIONS:

Although the percentage of subjects who quit smoking during the last 4 weeks of treatment was slightly higher in the EVT 302 group compared to placebo, the study failed to show any statistically or clinically meaningful difference between EVT 302 and placebo either in the presence or absence of NRT. However, the addition of NRT to EVT 302 and placebo did increase the rates of responders and showed a better performance compared to non-NRT groups across the majority of assessed efficacy variables.

All treatment groups showed a substantial and sustained decrease from baseline throughout the study in the average number of cigarettes smoked per day, with no relevant differences found among the four groups indicating homogeneity. Treatment with EVT 302, either alone or in the presence of NRT, did not lead to a worsening of smoking withdrawal symptoms and a clearly progressive improvement of smoking urges symptoms and smoking reinforcing and aversive effects was observed throughout the study across all groups. Subject satisfaction with study medication was high in all treatment groups and the majority of the subjects were willing to take EVT 302 again.

EVT 302 was safe and well tolerated. Most TEAEs were mild or moderate and were related to infections and infestations, nervous system disorders and gastrointestinal disorders. The addition of NRT tended to increase in the incidence of TEAEs, particularly for drug-related TEAEs for nervous system disorders; gastrointestinal disorders; general disorders and administration site conditions; and skin and subcutaneous tissue disorders. The incidence of drug-related abnormal LFTs and cardiovascular irregularities was low in all treatment groups, with no apparent increase when comparing either EVT 302 or placebo alone with NRT treatment groups. In this large population, no signs of a tyramine hypersensitivity reaction were observed.

DATE OF REPORT:

22 Jun 2009