2. SYNOPSIS

Name of Sponsor: Evotec Neurosciences GmbH	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **N/A**	**Volume:** **N/A**	
Name of Active Ingredient: EVT 101	**Page:** **N/A**	

Title of Study: A double blind, placebo controlled study to investigate the role of NMDA receptor NR2B subunit selective antagonism on cognitive functions and neurophysiology in healthy subjects as measured with MRI

Principal Investigator: [redacted]

Study Centres:

[redacted]

Publication (reference): None

Studied Period:	**Phase of Development:**
04 September 2007 (date of first enrolment) 18 December 2007 (date of last Follow-up)	Phase 1

Objectives:

Primary Objective:
To investigate neurophysiological changes following EVT 101 with fMRI during rest and cognitive tasks in young healthy male subjects.

To investigate the neuropsychological changes following EVT 101 using a validated battery of cognitive tasks, in young healthy male subjects.

To relate the effects of EVT 101 on fMRI signal to the effects on performance in cognitive tasks.

Secondary Objectives:
To determine plasma concentrations of EVT 101 in the subjects (pre-dose, 1, 1.5, 2, and 4h after dosing).

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Methodology:

This was a double-blind, placebo-controlled, single oral dose, randomised, intra-individual three-way cross-over study. Twenty eligible subjects were planned to be included for 16 to complete the study as per protocol. Each subject participated in three study periods separated by washout periods of 1 week. A washout period may have been extended to a maximum of 3 weeks in exceptional circumstances if a subject was unable to attend for a scheduled visit. For each period, subjects reported to the [redacted] on Day -1 and stayed overnight. The following morning they were transported to the Centre for Neuroimaging Science ("CNS") for subsequent procedures including study drug administration, fMRI, cognitive testing and a number of clinical measurements. Subjects stayed in the "CNS" from pre-dose until after approximately 6 hours post-dose when they were transported back to [redacted]. They stayed overnight at the [redacted] until 24 hours post-dose.

In each period, subjects were dosed with a single oral dose of either EVT 101 (8 mg), EVT 101 (15 mg) or matching placebo. Amongst other assessments, they were required to complete an fMRI scan in each period and a battery of cognitive tests which were undertaken at approximately 2 hours after dosing with EVT 101 (or matching placebo).

Number of Subjects (Planned and Analysed):

A total of about 20 healthy male volunteers were planned to be included for 16 to complete the study. Nineteen healthy male volunteers were actually included and enrolled on to the study. No subject withdrew from the study. All data were analysed.

Main Criteria for Inclusion:

Male subjects of any ethnic origin aged between 18 and 55 years, with a body mass index (BMI) between 19 and 29 kg/m^2 and in good health as determined by medical history, physical examination, electrocardiogram (ECG) and clinical chemistry. All subjects were required to give written informed consent.

Test Product, Dose and Mode of Administration, Batch Number:

EVT 101 capsules administered orally (8 mg [batch numbers: 07062, 07068, 07071, 07072, 07074, 07082] and 15 mg [batch numbers: 07062, 07068, 07071, 07072, 07074, 07082]) and matching placebo capsules (identical in size, weight and colour to their matching active capsules, batch numbers: 07062, 07068, 07071, 07072, 07074, 07082). Subjects attended a Follow-up visit 5-7 days after their last treatment period.

Duration of Treatment:

Subjects received a single dose of study medication on Day 1 of each of the 3 treatment periods. Each dose was separated by a washout period of at least 7 days.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

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Criteria for Evaluation:

Pharmacokinetic:
Blood samples were taken for the evaluation of EVT 101 in plasma at 1hr, 1.5hr, 2hrs and 4hrs post dosing.

Pharmacodynamic:
Change in fMRI Blood Oxygen Level Dependent signal under baseline conditions and during activation by cognitive tasks.

Change in regional Cerebral Blood Flow (rCBF, determined with ASL-MRI), after drug compared with placebo.

Performance scores in the cognitive tests.

Safety:
Safety included adverse event (AE) monitoring, safety laboratory blood tests (haematology, clinical chemistry and urinalysis), vital signs and 12-lead electrocardiogram (ECG). Renin, angiotensin II and aldosterone blood levels were also measured.

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Statistical Methods:

Pharmacokinetic:
EVT 101 PK concentration (ng/mL) was summarised descriptively at each time point measured using the following statistics: N (the number of subjects), mean, standard deviation, CV (coefficient of variation), median, minimum, and maximum by dose levels.

Pharmacodynamic:
fMRI:
The primary analysis method for statistical inference was to compare the activation maps for each subject on placebo with the same on drug, restricting the search volume to the task network. The set of voxel values resulting from each contrast constitutes a statistical parametric map of the t statistic. The t maps were transformed to the unit normal distribution and thresholded to account for multiple comparisons across the brain. This is the standard manner in which voxel-wise statistics are conducted over any brain volume. Additional ROI analyses specific to each task were also conducted.

Cerebral Blood Flow (CBF):

Regional values of resting state cerebral blood flow (rCBF) were determined using Arterial Spin labelling (ASL). The measurement was made by selectively inverting the MR signal of arterial blood and determining the effect of this inverted signal as it flows into the rest of the brain parenchyma.

Cognitive data:

Changes in performance on the paired associates learning task, episodic memory task and sustained attention were tested using repeated-measures ANOVA of accuracy of responses and latency to respond. Cognitive test data were also listed by subject and treatment.

Performances on the three cognitive tasks was also correlated with regions showing significant changes in rCBF following administration of EVT 101 to understand the potential functional significance of such changes in the context of this study. Exploratory analyses across the whole brain were also conducted.

Safety:
Safety data were summarised by treatment groups. No formal hypothesis testing was carried out.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic Results:

Plasma levels increased in a dose dependent manner with peak levels achieved by approximately 1.5 hours after administration. Mean maximum plasma concentrations reached were about 55 and 110 ng/mL with 8 and 15 mg, respectively.

Pharmacodynamic Results:

The BOLD fMRI analysis showed differential effects dependent on the task. For the episodic memory task there was an interaction between the depth and accuracy of encoding in the right parahippocampal region. For the learning task, there was an increase in the activation of the retrieval networks, while for the sustained attention task there was reduced activation of the response inhibition network. EVT 101 impaired task performance accuracy on the delayed memory task although performance on the paired associates learning task and sustained attention tasks was unchanged. The BOLD responses were not explained by variations in task performance. EVT 101 also produced clear increases in rCBF in the perigenual region of the cingulate cortex, without altering global rCBF.

Safety Results:

The results of this study showed that 8 mg EVT 101 and 15 mg EVT 101 were well tolerated. There was a low incidence of adverse events in all treatment groups. Although there appeared to be a small EVT 101 dose related increase in the frequency of adverse events, only one event (transient blurred vision in the 15 mg group) was considered by the Investigator to be related to study medication. All AEs were mild and no subject was withdrawn due to an AE.

There were no clinically significant differences between treatment groups in mean change from baseline in any haematology, clinical chemistry or hormone parameters. There were small but apparently dose-related increases in mean serum creatinine values and mean total protein values which were not considered clinically relevant. Only one subject had a transient increase in serum creatinine to slightly above the upper limit of normal following EVT 101 15 mg which had returned to within normal limits at the Follow-Up visit. Two subjects in the 8 mg group and 4 subjects in the 15 mg group had total protein values that increased to slightly above the upper limit of normal compared to none on placebo; these values returned to within normal limits at the Follow-up visit.

With regards to vital signs, there was a trend suggesting a slight increase in mean change in systolic blood pressure following dosing with EVT 101 15 mg compared with placebo although no subject had a clinically significant increase in blood pressure following dosing. With the exception of one subject who had mild transient orthostatic hypotension after EVT 101 15mg, there were no apparent differences between groups in diastolic blood pressure, postural changes in vital signs or ECG parameters. The results of all neurological examinations were normal.

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CONCLUSIONS :

- The fMRI analysis showed differential effects of EVT 101 dependent on task in healthy male subjects. For the episodic memory task, there was an interaction effect between depth and accuracy of encoding. For the learning task, there was an increase in the activation of the retrieval networks, while for the sustained attention task there was reduced activation of the retrieval inhibition network.
- There was increased regional cerebral blood flow compared to placebo in a discrete region of the anterior cingulate cortex perigenually. This data encourages further clinical work, potentially in a variety of diseases such as cognitive impairment, pain and mood disorder.
- Performance on the paired associates learning task and sustained attention task was unchanged by EVT 101 although there was some impairment in performance accuracy on the delayed memory task.
- Single oral doses of 8 mg and 15 mg EVT 101 were well tolerated in young healthy male subjects. There was a low incidence of AEs, all of which were mild and no subject was withdrawn due to an AE.
- There were no clinically significant changes in haematology, clinical chemistry or urinalysis parameters following single doses of EVT 101.
- Plasma levels of renin, aldosterone and angiotensin II appeared unaffected by single doses of EVT 101.
- There was a trend suggesting a small increase in mean systolic blood pressure after the 15 mg EVT 101 dose but no subject had a clinically significant increase in blood pressure. This trend was not seen with the 8 mg dose. With the exception of one subject (15 mg EVT 101) who had transient orthostatic hypotension, no other clinically significant changes were observed at either dose on vital signs or ECG parameters.
- Peak plasma concentrations of EVT 101 were observed approximately 1.5 hours post-dose and increased with dose.

Date of the Report: 27 November 2008