1 TITLE PAGE

Clinical Study Report – Avraham Pharmaceuticals Ltd.

Protocol number: CO17730

Title: A 36-month, multi-centre, randomized double-blind placebo-controlled study to evaluate the safety and efficacy of low-dose ladostigil in patients with mild cognitive impairment (MCI)

Investigational Product:	Ladostigil capsules
Indication:	Mild cognitive impairment
Study Design:	Multi-centre, randomized, double-blind, placebo-controlled, parallel-group
EUDRACT Number:	2011-004187-30
First Patient Screened:	30 January 2012
First Patient Enrolled:	17 February 2012
Last Patient Last Visit:	26 July 2016
Development Phase:	Phase 2
Name of Sponsor:	Avraham Pharmaceuticals Ltd. 42 Hayarkon Street, Northern Industrial Zone Yavneh, 81227 Israel
Author:	Jessica Prattner, Ph.D. – Medical Writer
Date of Report:	21 March 2017

The study was performed in compliance with the principles of Good Clinical Practice (GCP) guidelines as well as in accordance with all national, state and local laws of the appropriate regulatory authorities, including the archiving of essential documents.

2 SYNOPSIS

Name of Sponsor/Company: Avraham Pharmaceuticals Ltd. 42 Hayarkon Street, Northern Industrial Zone Yavneh, 81227 Israel **Name of Drug Product:** Ladostigil **Name of Drug Substance:** Ladostigil hemitartrate	Individual Study Table Referring to Clinical Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Title of Study: A 36-month, multi-centre, randomized double-blind placebo-controlled study to evaluate the safety and efficacy of low-dose ladostigil in patients with mild cognitive impairment (MCI)		
Study Centres: 1. Rambam Medical Centre, Haifa 2. Carmel Medical Centre, Haifa 3. Hadassah Har Hazhofim University Hospital, Jerusalem 4. Mental Health Centre, Be'er Sheva 5. Sheba Medical Centre, Ramat Gan 6. Sorasky Medical Centre, Tel Aviv 7. Medical University of Graz, Graz 8. General Hospital Hall, Hall in Tirol 9. Private Practice Vienna, Vienna 10. Study Centre Nordwest, Westerstede 11. Study Centre Emovis, Berlin 12. University Clinic, Magdeburg 13. Pharmacological Study Centre Chemnitz, Außenstelle Mittweida 14. Study Centre Leipzig, Leipzig 15. Edith Wolfson Medical Centre, Holon 16. Rabin Medical Centre, Petah Tikva		**Publication (reference):** Not applicable
Study Period: 30 January 2012 -26 July 2016		**Phase of Development:** Phase II
Objectives: The objectives of the study were as follows: <u>Primary objectives</u> • The primary objective of the study was to assess whether 10 mg ladostigil q.d. can slow or stop the conversion from MCI to AD during a three year treatment period compared to placebo. The primary endpoint was the percentage of patients that progressed from MCI to probable or possible AD according to NINCDS-ADRDA criteria. Conversion to AD was determined using CDR. • Time to conversion from MCI to AD was analysed by means of Kaplan Meier's survival method		

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Secondary objectives

- The effect of 10 mg ladostigil taken orally once daily on Geriatric Depression Scale (GDS), Neuropsychiatric Test Battery (NTB) and Disability Assessment in Dementia (DAD) compared to Baseline were determined as secondary outcomes.
- Safety of 10 mg ladostigil taken orally once daily was also evaluated.

Exploratory objectives

- The effect of 10 mg ladostigil q.d. versus placebo on changes (from Baseline) in different cognitive domains using NeuroTrax Mindstreams computerized cognitive battery.
- The effect of 10 mg ladostigil q.d. versus placebo, at 12, 24 and 36 months, on changes (from Baseline) in hippocampal, entorhinal cortex and whole brain volume using MRI. The effect of 10 mg ladostigil q.d. versus placebo on immunological parameters and on MAO-B inhibition and circulating DHPG as indication of MAO-A inhibition was evaluated.

Methodology:

This study was a 36-month, randomized, double-blind, placebo-controlled, parallel-group, multi-centre investigation. The study evaluated the safety and efficacy of 10 mg ladostigil taken orally once daily versus a matching placebo in patients with MCI. A total of 210 patients were recruited in about 15 study centres in Israel, Germany and Austria (16 sites were planned, but one site did not recruit any patients). The study consisted of a screening visit, followed by a 36-month double-blind treatment period. The primary objective of this study was to assess whether 10 mg ladostigil taken orally once daily can stop or slow conversion of MCI to AD during a three-year treatment period. Conversion to AD was determined by the Principal Investigator using the Clinical Dementia Rating and NINCDS-ADRDA criteria but if a patient showed distinct signs and symptoms of AD although the CDR score was below 1, the Principal Investigator could decide upon his experience, that the patient had converted to AD. Conversion ratios were determined for each treatment arm (ladostigil, placebo). Secondary objectives addressed the effect of ladostigil versus placebo on the Neuropsychiatric Test Battery, Disability Assessment in Dementia and Geriatric Depression Scale. Exploratory endpoints evaluated the effect of ladostigil versus placebo on a NeuroTrax Mindstreams computerized cognitive battery and on the atrophy of the hippocampus, on the volume of the entorhinal cortex and on the volume of the whole brain as assessed by MRI. Furthermore, the effect of 10 mg ladostigil versus placebo on immunological parameters and on platelet MAO-B inhibition and circulating DHPG as indication of MAO-A inhibition were also evaluated.

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Whenever a study participant converted to possible or probable AD, study medication or its corresponding placebo were discontinued and the patient was removed from the study and treated according to standard AD therapy.

Number of Patients (Planned and Analysed):
A total of 200 male and female patients with MCI were planned in this study. Two hundred and ten (210) patients were enrolled, 112 remained in the study for the whole 3-Year period, 209 were eligible for the ITT population, 202 were eligible for the mITT population, 178 were eligible for the PP population, 133 were eligible for the mPP population and 210 were eligible for the safety population in this study.

Diagnosis and Criteria for Inclusion:

Patients were eligible for the study if they met the following iclusion criteria and no exclusion criteria:

Inclusion criteria:

1. Men and women (non-childbearing potential) with a diagnosis of MCI.
2. Abnormal memory function was evaluated by Verbal Paired Associates from the Wechsler Memory Scale – Revised. Normal values for healthy adults in two age cohorts are: a) 50-70 years 19.7 (SD = 2.9) and b) 75-95 years 18.3 (SD = 2.8). Patients that score ≤ 18 were included.
3. Clinical Dementia Rating (CDR) score of 0.5 (Memory box score 0.5 or 1, no box score greater than 1).
4. Mini-Mental State Examination (MMSE) > 24.
5. General cognition and functional performance sufficiently preserved such that a diagnosis of AD could be excluded by the site physician at the time of the screening visit.
6. No significant cerebrovascular disease indicated by Modified Hachinski Ischaemic Score equal to or below 4.
7. Age 55 - 85 years, because no significant correlation of cognition and Schelten's score has been observed above the age of 85.
8. Geriatric Depression Scale (GDS) of less than or equal to 5.
9. An available informer who had frequent contact with the patient (*e.g.* an average of 10 hours per week or more) who agreed to monitor administration of study drug, to observe the patient for adverse events, and to accompany the patient to clinical visits during the

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study, if the presence of the informer was required.

10. All patients did undergo an MRI scan after the screening visit, *i.e.* during the screening period, irrespective of MRIs having been performed prior to entry into the study. MRI findings had to be consistent with a diagnosis of MCI.
11. Central rating of medial temporal lobe according to Scheltens scale. The right and left medial temporal structures were rated separately, and an overall estimate was created using the average of the two ratings. An average score > 1 was required to make patients eligible for the study.
12. Adequate visual and auditory acuity had to be given to allow neuropsychological testing.
13. Good general health status acceptable for a participation in a 36-month clinical study, with no additional diseases expected to interfere with the study.
14. ECG without clinically significant abnormalities according to exclusion criterion 6.
15. Patient was not pregnant, lactating, or of childbearing potential (*i.e.* women had to be two years post-menopausal or surgically sterile).
16. Signed informed consent by patient and informer prior to any study specific procedure

Exclusion criteria:

1. Failure to perform screening or baseline examinations.
2. Any significant neurologic disease other than suspected MCI.
3. MRI exclusion criteria which allow for mild concomitant vascular lesions were:
   - Thromboembolic infarction
   - Other focal lesions which may be responsible for the cognitive status of the patient such as infectious disease, space-occupying lesions, normal pressure hydrocephalus or any other abnormalities associated with significant central nervous disease.
   - More than one lacunar infarct defined as a focal lesion of CSF signal intensity with a diameter of less than 1.5 cm in any dimension.
   - Any lacunar infarct in a strategically important location such as the thalamus, hippocampus of either hemisphere, head of the left caudate.
   - White matter lesions involving more than 25% of the hemispheric white matter.
   - Implants such as pacemakers, insulin pumps, cochlear implants, nerve stimulators, implantable cardioverter defibrillators, and other medical implants that were certified for MRI.

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- Ferromagnetic foreign bodies such as shell fragments needed to be considered on an individual basis
- Metallic implants that could cause artifacts and RF induced heating such as surgical prostheses or aneurysm clips needed to be considered on an individual basis

4. Clinical or laboratory findings consistent with:
   - Central nervous system diseases such as those resulting from severe head trauma, tumours, subdural haematoma or other space occupying processes, etc.
   - Seizure disorder.
   - Other infectious, metabolic or systemic diseases affecting central nervous system (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, serum electrolytes out of normal range, juvenile onset diabetes mellitus, etc.)
5. History or evidence of schizophrenia or bipolar disorder (DSM IV criteria). Active major depression.
6. Clinically significant advanced or unstable diseases that could interfere with primary or secondary variable evaluations, and which may bias the assessment of the clinical or mental status of the patient or put the patient at special risk, such as:
   - Malignant tumours within the last five years except skin malignancies (other than melanoma) or indolent prostate cancer
   - Metastases
   - History of myocardial infarction within one year prior to Screening or unstable or severe cardiovascular disease including angina or congestive heart failure with symptoms at rest.
   - Uncontrolled hypertension (systolic pressure > 170 mmHg or diastolic pressure > 100 mmHg) at rest.
   - Bradycardia (persistent heart beat < 50/min) or tachycardia (persistent heart beat > 100/min)
   - AV block (type II / Mobitz II and type III), congenital long QT syndrome, sinus node dysfunction or prolonged QTcB-interval (males > 450 msec, females > 470 msec)
   - Clinically significant obstructive pulmonary disease or asthma.
   - Clinically significant laboratory findings that indicated abnormalities in blood biochemistry, blood haematology or urinalysis.
   - Uncontrolled diabetes mellitus defined by HbA1c > 8.5.
   - Clinically significant liver disease, coagulopathy, or vitamin K deficiency within the past two years prior to Screening.

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- Renal insufficiency (serum creatinine >2mg/dl or creatinine clearance ≤ 45 mL/min according to Cockgroft-Gault formula). In case of creatinine clearance ≤45mL/min, an alternative verification of the renal function had to be completed using cystatin C analysis. In case of normal level of cystatin C the patient was included.

7. Any prior use of medications approved by local authorities for the treatment of AD (*e.g.* tacrine, donepezil, rivastigmine, galantamine, memantine or other newly approved medications).
8. Disability that could prevent the patient from completing all study requirements (*e.g.* blindness, deafness, severe language difficulty, *etc*.)
9. Women who were fertile and of child bearing potential.
10. Chronic daily intake of antidepressants as noted in Section 9.5. of the clinical study protocol.
11. Suspected or known drug or alcohol abuse, *i.e*. more than approximately 60 g alcohol (approximately 1 litre of beer or 0.5 litre of wine) per day indicated by elevated MCV significantly above normal value at Screening.
12. Suspected or known allergy to any components of the study treatments.
13. Enrolment in another investigational study or intake of investigational drug within the previous three months.
14. Any condition (e.g. epilepsy), which in the opinion of the investigator made the patient unsuitable for inclusion.

Test Product, Reference Product. Dose and Mode of Administration, Batch Number:
All patients received dry blend, powder-filled hard gelatin capsules once daily through oral administration containing 10 mg ladostigil or placebo with the batch/Lot numbers 21861001, L0307076 and L0307077 (ladostigil and placebo had the same batch numbers).

Duration of Treatment:
The total duration of the study was 36 months for each patient, unless the patient converted to AD or dropped out

Criteria for Evaluation:
Conversion to AD, defined as the percentage of patients that progressed from MCI to probable or possible AD as determined by assessment of CDR over a three-year treatment period.

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The effect of ladostigil on changes from baseline was investigated by several assessments, the neuropsychological test battery (NTB), the geriatric depression scale (GDS), the disability assessment in dementia (DAD) and NeuroTrax Mindstream, a computerized test battery assessing different cognitive domains of the brain.

The effect of ladostigil on hippocampal, entorhinal cortex and whole brain volume was assessed by MRI.

The effect of ladostigil on certain immunological parameters was assessed by laboratory tests.

The effect of ladostigil on MAO-B inhibition in platelets and circulating DHPG as indication of MAO-A inhibition should have been assessed by immunological laboratory tests. The analysis was not performed.

Safety measurements were: adverse events, physical and neurological examination, changes in vital signs, 12-lead ECG, safety laboratory and urinalysis.

Upon verification of a clinical diagnosis of AD by Investigator decision or means of CDR, treatment of patients was discontinued, and the patient was removed from the study thus becoming eligible to receive standard-of-care AD treatment.

Two interim analyses were performed: the first one after 146 patients had completed their first year of treatment and Visit 4 entered into the eCRF (data export date: 17 June 2014) and the second one after 126 patients had completed their second year of treatment and Visit 6 entered into the eCRF (data export date: 01 July 2015).

Statistical Methods:

Primary Objective

Time to conversion to AD – the time to conversion was analysed by means of Kaplan-Meier's survival method.

Secondary Objectives

GDS – the GDS score was analysed using ANCOVA and repeated measures mixed model and using categories with chi square test.

DAD - The total DAD score as well as subscores were analyzed (including change from baseline) using ANCOVA and repeated measures mixed model.

NTB - Between groups analysis for total Z score as well as subscores were conducted for change from baseline score using an ANCOVA and repeated measures mixed model.

Exploratory Objectives

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NTX - Between groups analysis for total as well as sub scores were conducted for change from baseline score using an ANCOVA and repeated measures mixed model.
Composite cognitive score using NTB and NTX scores - Between groups analysis for total as well as sub scores were conducted for change from baseline score using an ANCOVA and repeated measures mixed model.
MRI – Total brain volume and right and left hippocampus volume and right and left entorhinal cortex was analyzed (including change from baseline) using an ANCOVA and repeated measures mixed model.
Immunological parameters - All immunological parameters were analyzed (including change from baseline) using ANCOVA and repeated measures mixed model.
CDR global score - Shift tables were prepared for baseline and at each visit wherever captured. Global Score as well as subscores were analyzed (including change from baseline) using ANCOVA and repeated measures mixed model.
CDR sum-of-boxes was analyzed (including change from baseline) using ANCOVA and repeated measures mixed model.
MMSE – It was analyzed (including change from baseline) using ANCOVA and mixed model.

Summary and Conclusions:
Efficacy

Primary Objective
The conversion rate from MCI to Alzheimer's Disease was not significantly different between the ladostigil treatment group and the placebo treatment group.

- After 3 years treatment with ladostigil: 14 AD converters were reported (conversion rate of 0.14) in the mITT population
- After 3 years treatment with placebo: 21 AD converters were reported (conversion rate of 0.20) in the mITT population

Secondary Objectives
GDS - No significant difference between the ladostigil treatment group and the placebo treatment group was observed in the whole mITT population after three years. The repeated measures mixed model gave a p-value of 0.1215, ANCOVA (MI) gave a p-value of 0.4361.
DAD - No significant difference between the ladostigil treatment group and the placebo treatment group was observed in the whole mITT population after three years. The repeated measures mixed model gave a p-value of 0.5007 for DAD total score, ANCOVA (MI) gave a p-value of 0.4804 for DAD total score.

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NTB - No significant difference between the ladostigil treatment group and the placebo treatment group was observed in the whole mITT population after three years. The repeated measures mixed model gave a p-value of 0.4263 for NTB Z-Score, ANCOVA (MI) gave a p-value of 0.3659 for NTB Z-Score.

Exploratory Objectives

Whole brain volume - A significant effect of ladostigil was observed on whole brain volume. After a treatment period of three years, the atrophy of the whole brain was significantly smaller in patients that received ladostigil compared to patients that received placebo. The repeated measures mixed model gave a p-value of 0.0367, ANCOVA (MI) gave a p-value of 0.0758.

- After 3 years treatment with ladostigil: the mean change in percent of whole brain volume was -2.32 (±2.33)
- After 3 years treatment with placebo: the mean change in percent of whole brain volume was -3.28 (±2.19)

No significant treatment effect was determined for the exploratory objectives NeuroTrax Mindstreams, Composite Cognitive Scores, hippocampal and entorhinal cortex volume, immunological parameters, CDR global score, CDR SOB or MMSE score.

Safety

No treatment effect was observed in any of the safety parameters. No AE or SAE was considered related to ladostigil treatment. Over the study duration of three years, 170 patients out of 210 experienced at least one AE.

Following the treatment with ladostigil:

- One (1) death was reported after treatment with ladostigil, with an unlikely relationship to the study treatment
- 85 patients (82.5%) experienced 428 AEs
- No AE was considered related to ladostigil treatment
- 1 patient (1.0%) reported an AE that was considered probably related to ladostigil treatment (mild alcohol intolerance)
- 18 patients (17.5%) reported at least one AE that was considered possibly related to ladostigil treatment.
- 26 patients (25.2%) experienced 51 SAEs
- 1 patient (1%) reported a persistent or significant disability / incapacity after an SAE

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- 1 patient (1%) reported a medically significant diagnosis or event

Following the treatment with placebo:

- 85 patients (79.4%) experienced 380 AEs
- 1 patient (0.9%) reported an AE that was considered related to placebo treatment (Diarrhea)
- 4 patients (3.7%) reported at least an AE that was considered probably related to placebo treatment (Excess sweating, Allergic reaction, Constipation, Tiredness, Depressed mood and Abnormal stools)
- 28 patients (26.1%) experienced 45 SAEs
- 9 patients (8.8%) reported 10 medically significant diagnosis or events.

There were no clinically significant findings with an obvious treatment related, or study assessment related abnormality reported for laboratory safety values, urinalysis, vital signs, physical examination, neurological Examination or ECG data. Ladostigil has been shown to be safe and well tolerated.

Date of Report: 21 March 2017