Clinical trial results:
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)

Summary

EudraCT number	2011-004187-30
Trial protocol	AT DE
Global end of trial date	26 July 2016

Results information

Result version number	v1 (current)
This version publication date	20 December 2017
First version publication date	20 December 2017
Summary attachment (see zip file)	Synopsis (CO17730-Synopsis_Avraham-Ladostigil-final-version 1.pdf)

Trial information

Trial identification

Sponsor protocol code	CO17730

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Avraham Pharmaceuticals Ltd.
Sponsor organisation address	42 Hayarkon Street, Yavneh, Israel, 81227
Public contact	Moti Hacham, Chief Financial & Operation Officer., Avraham Pharmaceuticals Ltd. 42 Hayarkon st, Yavneh, 81227, +972 8-932-4000, motih@cls.co.il
Scientific contact	Moti Hacham, Chief Financial & Operation Officer., Avraham Pharmaceuticals Ltd. 42 Hayarkon st, Yavneh, 81227, +972 8-932-4000, motih@cls.co.il

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2016
Global end of trial reached?	Yes
Global end of trial date	26 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to assess whether 10 mg ladostigil q.d. can slow or stop the conversion from Mild Cognitive Impairment (MCI) to Alzheimer's disease (AD) during a three year treatment period compared to placebo.
The primary endpoint was the percentage of subjects that progressed from MCI to probable or possible AD according to NINCDS-ADRDA criteria. Conversion to AD was determined using Clinical Dementia Rating (CDR).

Protection of trial subjects:

NA

Background therapy:

NA

Evidence for comparator:

A placebo group was required in order to differentiate any investigational drug effect from any improvement that could occur solely due to the close care and medical oversight given to patients under trial conditions.

Patients assigned to the placebo group did not abandon standard medical treatment, since there are no currently approved drugs for treatment of MCI

Actual start date of recruitment	01 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 97
Country: Number of subjects enrolled	Austria: 47
Country: Number of subjects enrolled	Germany: 66
Worldwide total number of subjects	210
EEA total number of subjects	113

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	31
From 65 to 84 years	175
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from January 2012 until July 2013. It was planned to recruit 50 patients in Austria, 50 patients in Germany and 100 patients in Israel.

Pre-assignment

Screening details:

Patients had to be diagnosed with MCI and had to fulfill the following main criteria:
No AD with NINCDS-ADRDA diagnosis "none"
WMS-VerPA <18
CDR 0.5
MMSE >24
Modified Hachinski Ischaemic Scale ≤4
Age 55-85
GDS ≤5
Caretaker with frequent contact to patient
Scheltens score >1
Adequate visual and auditory acuity
good health, not pregnant

Pre-assignment period milestones

Number of subjects started	413[1]
Number of subjects completed	210

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failures: 203

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Only subjects that succesfully completed the Screening period were assigned to a treatment, and randomized (enrolled). However, all subjects that underwent screening assessments signed an informed consent

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

There were no differences between ladostigil capsules and placebo capsules in shape, size, colour or weight. The manufacturing organization was strictly independent from the sponsor's activities. No accidental unblinding by laboratory measurements was possible.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

100 patients were planned to receive placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Placebo once daily in the morning

Arm title	Ladostigil

Arm description:

100 patients were planned to receive the active ingredient

Arm type	Experimental
Investigational medicinal product name	Ladostigil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10mg Ladostigil once daily in the morning

Number of subjects in period 1	Placebo	Ladostigil
Started	107	103
Completed	55	57
Not completed	52	46
Consent withdrawn by subject	13	19
Caretaker withdrew consent	1	1
Physician decision	3	2
Other	1	1
Death	-	1
AE/SAE	14	7
Sponsor decision	1	-
early termination due to AD conversion	17	12
Protocol deviation	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
100 patients were planned to receive placebo	
Reporting group title	Ladostigil
Reporting group description:	
100 patients were planned to receive the active ingredient	

Reporting group values	Placebo	Ladostigil	Total
Number of subjects	107	103	210
Age categorical Units: Subjects			
Adults (18-64 years)	16	15	31
From 65-84 years	89	86	175
85 years and over	2	2	4
Age continuous Units: years			
arithmetic mean	71.4	71.3	
standard deviation	± 6.8	± 6.3	-
Gender categorical Units: Subjects			
Female	41	36	77
Male	66	67	133

Subject analysis sets	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized patients.	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All analyses predominantly used the modified Intent-To-Treat (ITT) patient population, which included all patients who received at least one dose of medication and completed at least one post-Baseline assessment.	

Reporting group values	Safety	mITT	
Number of subjects	210	202	
Age categorical Units: Subjects			
Adults (18-64 years)	31	30	
From 65-84 years	175	168	
85 years and over	4	4	
Age continuous Units: years			
arithmetic mean	71.3	70.8	

standard deviation	± 6.5	± 7.1	

Gender categorical Units: Subjects			
Female	77	76	
Male	133	126	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
100 patients were planned to receive placebo	
Reporting group title	Ladostigil
Reporting group description:	
100 patients were planned to receive the active ingredient	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized patients.	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All analyses predominantly used the modified Intent-To-Treat (ITT) patient population, which included all patients who received at least one dose of medication and completed at least one post-Baseline assessment.	

Primary: Time to Conversion from MCI to AD

End point title	Time to Conversion from MCI to AD
End point description:	
The CDR was developed for the evaluation of staging severity of dementia. It was developed primarily for the use in persons with dementia of the Alzheimer type and it can also be used to stage dementia in patients with other illnesses. CDR scores are as follows: 0 = Normal 0.5 = Very Mild Dementia 1 = Mild Dementia 2 = Moderate Dementia 3 = Severe Dementia Thus, scores of ≥ 1 are indicative of conversion to AD. After treatment with ladostigil, 14 AD converters were reported and after treatment with placebo, 21 AD converters were reported, resulting in a conversion rate of 0.14 for ladostigil patients and a conversion rate of 0.20 for placebo patients over the whole study period of 36 months. The conversion rate from MCI to Alzheimer's Disease was not significantly different between the ladostigil treatment group and the placebo treatment group.	
End point type	Primary
End point timeframe:	
The CDR assessment was performed at baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months regularly over the whole study period.	

End point values	Placebo	Ladostigil	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	103	99	202	
Units: Numbers of Patients that converted to AD	21	14	35	

Statistical analyses

Statistical analysis title	Kaplan-Meier's survival method

Statistical analysis description:

The Kaplan Meier's survival curves for the two treatments were compared using the Logrank test.

Comparison groups	Ladostigil v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Secondary: The Effect of 10 mg ladostigil on GDS

End point title	The Effect of 10 mg ladostigil on GDS

End point description:

The GDS is a screening test for depressive symptoms in the elderly. This test is ideal for evaluating the clinical severity of depression. No significant difference between the ladostigil treatment group and the placebo treatment group could be observed in the whole mITT population after three years.

End point type	Secondary

End point timeframe:

The GDS was assessed at Baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months Visit, regularly over the whole study period (36 months).

End point values	Placebo	Ladostigil	Safety	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	107	103	210	
Units: GDS Score				
number (not applicable)				
GDS <=5	107	103	210	
GDS >5	7	4	11	

Statistical analyses

No statistical analyses for this end point

Secondary: The effect of 10 mg ladostigil on DAD

End point title	The effect of 10 mg ladostigil on DAD

End point description:

The DAD was developed to fulfil the need for a disability measure designed specifically for the assessment of disability in community residing individuals with cognitive defects. The DAD scale was used to measure functional abilities in activities of daily living quantitatively and to monitor these abilities throughout the study. No significant difference between the ladostigil treatment group and the placebo treatment group could be observed in the whole mITT population after three years.

End point type	Secondary

End point timeframe:

The DAD was assessed at Baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months Visit, regularly over the whole study period (36 months).

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: DAD Score				
arithmetic mean (standard deviation)	98.5 (± 4.1)	97.2 (± 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of 10 mg ladostigil on NTB

End point title	The Effect of 10 mg ladostigil on NTB

End point description:

The NTB is a well evaluated test instrument to measure drug efficiency in patients with cognitive impairment. It is a sensitive and reliable measure of cognitive change in patients with mild to moderate cognitive impairment. No significant difference between the ladostigil treatment group and the placebo treatment group could be observed in the whole mITT population after three years.

End point type	Secondary

End point timeframe:

The NTB was assessed at Baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months Visit, regularly over the whole study period (36 months).

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: z-scores for total NTB				
arithmetic mean (standard deviation)	0.458 (± 0.757)	0.350 (± 0.835)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of 10 mg ladostigil on NeuroTrax Mindstreams

End point title	The Effect of 10 mg ladostigil on NeuroTrax Mindstreams

End point description:

The NeuroTrax Mindstreams Test requires patient interaction with the computer and provides normatively based and raw score results for each patient. The test is very patient-friendly and requires little orientation. Although the test is performed on a computer, it does not require the patient to know how to use one. NeuroTrax Mindstreams assesses the patient´s cognitive function by precisely measuring the patient´s performance on a series of interactive tests – revealing both the accuracy of the responses and the patient´s cognitive function by measuring the reaction times in milliseconds. No

significant difference between the ladostigil treatment group and the placebo treatment group could be observed in the whole mITT population after three years.

End point type	Other pre-specified

End point timeframe:

The NeuroTrax was assessed at Baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months Visit, regularly over the whole study period (36 months).

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: Global Cognitive Score				
arithmetic mean (standard deviation)	100 (± 12)	100 (± 14)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of 10 mg ladostigil on Composite Cognitive Scores

End point title	The Effect of 10 mg ladostigil on Composite Cognitive Scores

End point description:

The Composite Cognitive Score is a combination of NTB and NeuroTrax scores. No significant difference between the ladostigil treatment group and the placebo treatment group could be observed in the whole mITT population after three years.

End point type	Other pre-specified

End point timeframe:

The Composite Cognitive Scores were evaluated at Baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months Visit, regularly over the whole study period (36 months).

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: Composite Cognitive Score				
arithmetic mean (standard deviation)	0.151 (± 0.787)	0.476 (± 0.835)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of 10 mg ladostigil on hippocampal, entorhinal cortex and whole brain volume

End point title	The Effect of 10 mg ladostigil on hippocampal, entorhinal

	cortex and whole brain volume

End point description:

A significant effect of ladostigil could be 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.

End point type	Other pre-specified

End point timeframe:

The MRI Scans for determination of brain volume were performed at Baseline and at the 12 months, 24 months and 36 months Visit.

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: mm^3				
arithmetic mean (standard deviation)	1293721 (± 92130)	1313140 (± 85858)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of 10 mg ladostigil on Immunological Parameters

End point title	The Effect of 10 mg ladostigil on Immunological Parameters

End point description:

Serum and peripheral blood mononuclear cells (PBMCs) were used for determination of immunological parameters. PBMCs were analysed by FACS for leukocyte subpopulations (CD4: T-effector and T-regulatory, CD8, monocytes, B cells, NK) and were stimulated with anti-CD3 to activate T cells. Anti-CD3 stimulation was performed also in the presence of increasing concentrations of methylprednisolone (MP). Supernates were collected at 24-72 hours and cytokines (primarily T-cell derived)/chemokines were measured by ELISA array. Furthermore, PBMCs were stimulated by LPS (0.1, 1, 10 and 100 ng/ml) or A-beta/heat shock protein (HSP) for 24 hours. Cytokines/chemokines were measured by ELISA arrays IL-1b, TNF-a, IL-6, IFN-g, IL-10 TGF-b IL-12 and nitric oxide.
A statistically significant difference between placebo and ladostigil treatment was shown for T-helper cells only and the repective data are presented.

End point type	Other pre-specified

End point timeframe:

Measurements of Immunological parameters were performed at Baseline V1 and at V4, V6 and V8. Due to organizational procedures, blood sampling for immunological assessments was done only at study sites in Israel.

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	47		
Units: cell count				
arithmetic mean (standard deviation)	39.9 (± 9.8)	44.5 (± 12.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of 10 mg ladostigil on Global CDR and CDR sum-of-boxes Score

End point title	The Effect of 10 mg ladostigil on Global CDR and CDR sum-of-boxes Score

End point description:

The Clinical Dementia Rating (CDR) was used to monitor the clinical staging of dementia. This was done via characterizing six domains of cognitive and functional performance via the 5-point scale of the CDR. No significant difference between the ladostigil treatment group and the placebo treatment group could be observed in the whole mITT population after three years.

End point type	Other pre-specified

End point timeframe:

The CDR and CDR Sum of boxes was assessed at Baseline and at 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months Visit, regularly over the whole study period (36 months).

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: Patient numbers as percentage				
number (not applicable)				
Score 0	16	7		
Score 0.5	82	92		
Score 1	2	2		
SCore 1.5	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of 10 mg ladostigil on MMSE score

End point title	The Effect of 10 mg ladostigil on MMSE score

End point description:

The MMSE is a frequently used screening instrument for cognitive impairment. The instrument provides for evaluation of orientation, memory, attention, concentration, naming, repetition, comprehension, ability to create a sentence and to copy two intersecting polygons. It was used to exclude severe cognitive impairment indicated by a score lower than 24. The highest (best) score is 30. No significant difference between the ladostigil treatment group and the placebo treatment group could be observed in

the whole mITT population after three years.

End point type	Other pre-specified

End point timeframe:

The MMSE was assessed at Baseline and at the 36 months visit or early termination visit.

End point values	Placebo	Ladostigil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: MMSE Score				
arithmetic mean (standard deviation)	27.2 (± 3.2)	27.7 (± 2.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After Baseline, all new findings or worsening of a pre-existing finding (if considered clinically significant) had to be reported as Adverse event. Data pertaining to AEs were collected during each study visit.

Adverse event reporting additional description:

At each study visit, the Investigator asked a general question, e.g."Have you experienced any other/new health problems since your last visit?" Furthermore, clinically significant findings of the physical examination, neurological examination, vital signs, ECG, laboratory assessments and Urinalysis were considered AEs:

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

All Patients randomized to receive placebo

Reporting group title	Ladostigil

Reporting group description:

All patients randomized to receive Ladostigil

Serious adverse events	Placebo	Ladostigil	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 107 (26.17%)	26 / 103 (25.24%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			

subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	4 / 107 (3.74%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 107 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 107 (1.87%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Cataract			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Umbilical hernia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic floor muscle weakness			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Ladostigil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 107 (79.44%)	85 / 103 (82.52%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 107 (2.80%)	6 / 103 (5.83%)	
occurrences (all)	3	6	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	6 / 107 (5.61%)	4 / 103 (3.88%)	
occurrences (all)	10	5	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 107 (5.61%)	7 / 103 (6.80%)	
occurrences (all)	6	8	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 107 (6.54%)	4 / 103 (3.88%)	
occurrences (all)	8	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 107 (6.54%)	8 / 103 (7.77%)	
occurrences (all)	7	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 107 (3.74%)	7 / 103 (6.80%)	
occurrences (all)	4	10	
Back pain			
subjects affected / exposed	10 / 107 (9.35%)	6 / 103 (5.83%)	
occurrences (all)	10	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 107 (12.15%)	11 / 103 (10.68%)	
occurrences (all)	15	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported