Clinical trial results:
FASE IV-II CLINICAL TRIAL, PROOF OF CONCEPT, RANDOMIZED, SIMULATED CONTROLLED TREATMENT, DOUBLE BLINDED AND UNICENTRIC WITH TWO PARALLEL GROUPS, TO EVALUATE SAFETY AND EFFICACY OF INTRAVITREAL ADMINISTRATION OF ETAMSILATO IN THE IMPROVEMENT OF VISUAL ACUITY IN PATIENTS WITH AGE RELATED MACULA DEGENERATION.

Summary

EudraCT number	2014-005259-20
Trial protocol	ES
Global end of trial date	15 September 2017

Results information

Result version number	v1 (current)
This version publication date	05 August 2018
First version publication date	05 August 2018
Summary attachment (see zip file)	Preliminary results (Final Report - PRELIMINARY RESULTS OF ETAMSYLATE IN ARMD.pdf)

Trial information

Trial identification

Sponsor protocol code	OFT-ETAMSILATO-4.2.1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Investigacion Independiente
Sponsor organisation address	C/ Cuesta del Sagrado Corazón nº 4, Madrid, Spain, 28016
Public contact	Rocio Garcia Cañamaque, León Research S.L., 0034 987261064, rgcanamaque@leonresearch.es
Scientific contact	Rocio Garcia Cañamaque, León Research S.L., 0034 987261064, rgcanamaque@leonresearch.es

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	01 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Stablish the efficacy after 4 weeks of a unique intravitreal injection with Etamsilato in the improvement of the visual acuity in patients diagnosed with dry or wet aged related macular degeneration disease

Protection of trial subjects:

To avoid having discomfort or pain with the injection in the eye (intravitreal), an anesthetic eye drop will be applied. Thus, the patient will not feel any pain or discomfort (PATIENTS WILL NOT BE ABLE TO DISTINGUISH IF THEY RECEIVE A REAL OR SIMULATED INJECTION)

Background therapy:

In the control group, the investigator will simulate giving patients the injection, using a blunt needle that does not penetrate the eyeball.

Evidence for comparator: -

Actual start date of recruitment	02 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
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)	5
From 65 to 84 years	30
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The present report presents the clinical results of a complete study, including three clinical trials, with patients recruited in a period of 24 months approximately. The PI will recruit patients, in chronological order according to their private consultation, when they meet the selection criteria specified in the study protocol.

Pre-assignment

Screening details:

Patients who are included in the study MUST meet all the inclusion criteria and MUST NOT present any of the exclusion criteria.
Database includes 48 patients, of which 4 of them were finally not considered as they were screen failures.

Period 1

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

Blinding implementation details:

Patients will not know what treatment they receive. In the control group, the specialist will simulate giving them the injection, using a blunt needle that does not penetrate the eyeball.
The specialist who evaluates the patients (interpreting the data required for this study) will not know what treatment each patient has received. Therefore, it is not the same specialist who administers the treatments, since he / she would know which injections are real or which are feigned.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

Patients receive etamsylate administration

Arm type	Experimental
Investigational medicinal product name	DICYNONE 250 mg/2 ml
Investigational medicinal product code	PRD437914
Other name	B02BX01
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

A single intravitreal injection of 18.75 mg of etamsylate (150 µL).

Arm title	Control

Arm description:

The specialist will simulate giving patients the injection, using a blunt needle that does not penetrate the eyeball

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Treatment	Control
Started	21	23
Completed	16	15
Not completed	5	8
Consent withdrawn by subject	3	-
Protocol deviation	2	8

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Patients receive etamsylate administration	
Reporting group title	Control
Reporting group description:	
The specialist will simulate giving patients the injection, using a blunt needle that does not penetrate the eyeball	

Reporting group values	Treatment	Control	Total
Number of subjects	21	23	44
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	76.286	78.087	
standard deviation	± 10.5363	± 10.4920	-
Gender categorical			
Units: Subjects			
Female	17	19	36
Male	4	4	8
eye to try selected			
Units: Subjects			
Left	10	14	24
Rigth	11	9	20
AMD type			
Units: Subjects			
Dry	7	8	15
Exudative	14	15	29
Ethnicity			
Units: Subjects			
White / Caucasian	21	22	43
No data	0	1	1
Employment situation			
Units: Subjects			
Work	0	1	1
Retired	18	21	39

No data	3	1	4
Family history with AMD Units: Subjects			
Yes	3	0	3
No	18	23	41
Smoking habit Units: Subjects			
former smoker	6	6	12
smoker	1	0	1
non smoker	13	16	29
No data	1	1	2
systemic pathologies Units: Subjects			
Any	12	10	22
High Blood Pressure (HBP)	2	2	4
Diabetes (DBT)	0	1	1
Chronic obstructive pulmonary disease (COPD)	0	1	1
Cardiovascular disease (CVD)	1	0	1
HIPERCOLESTEROLEMIA (HCOL)	2	1	3
Osteoporosis (OST)	1	0	1
HBP/HCOL	0	3	3
DTB / HBP / CVD	0	1	1
DTB / HBP/ CVD / HCOL	0	1	1
DTB / HBP/ HCOL	0	1	1
HBP/ HCOL	2	0	2
No data	1	2	3
LogMAR			
Logarithm of the Minimum Angle of Resolution. The visual reference angle is 20/20, which is the normal view, or the standard value, corresponding to a zero value of logMAR.			
Units: logMAR			
arithmetic mean	0.5515	0.6255	
standard deviation	± 0.38043	± 0.27131	-
punctuation by letters			
Indicates the number of letters that are identified correctly. The higher this score, the better the visual acuity			
Units: Number of letters			
arithmetic mean	54	49.100	
standard deviation	± 14.2478	± 12.6070	-

Subject analysis sets

Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: During the entire study, only one patient presented an Adverse Event (control group): elevated intraocular pressure	
Subject analysis set title	Analysis group by intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: valid assessment of visual acuity.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

There are a large number of patients with significant deviations, so we have to work with the analysis group per protocol, evaluable patients who meet the inclusion criteria and perform a valid follow-up.

Reporting group values	Safety	Analysis group by intention to treat	Per protocol
Number of subjects	44	41	31
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	36		
Male	8		
eye to try selected Units: Subjects			
Left	24		
Rigth	20		
AMD type Units: Subjects			
Dry	15		
Exudative	29		
Ethnicity Units: Subjects			
White / Caucasian	43		
No data	1		
Employment situation Units: Subjects			
Work	1		
Retired	39		
No data	4		
Family history with AMD Units: Subjects			
Yes	3		
No	41		
Smoking habit Units: Subjects			
former smoker	12		
smoker	1		

non smoker	29		
No data	2		
systemic pathologies Units: Subjects			
Any	22		
High Blood Pressure (HBP)	4		
Diabetes (DBT)	1		
Chronic obstructive pulmonary disease (COPD)	1		
Cardiovascular disease (CVD)	1		
HIPERCOLESTEROLEMIA (HCOL)	3		
Osteoporosis (OST)	1		
HBP/HCOL	3		
DTB / HBP / CVD	1		
DTB / HBP/ CVD / HCOL	1		
DTB / HBP/ HCOL	1		
HBP/ HCOL	2		
No data	3		
LogMAR			
Logarithm of the Minimum Angle of Resolution. The visual reference angle is 20/20, which is the normal view, or the standard value, corresponding to a zero value of logMAR.			
Units: logMAR arithmetic mean standard deviation	±	±	±
punctuation by letters			
Indicates the number of letters that are identified correctly. The higher this score, the better the visual acuity			
Units: Number of letters arithmetic mean standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Patients receive etamsylate administration	
Reporting group title	Control
Reporting group description:	
The specialist will simulate giving patients the injection, using a blunt needle that does not penetrate the eyeball	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
During the entire study, only one patient presented an Adverse Event (control group): elevated intraocular pressure	
Subject analysis set title	Analysis group by intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
valid assessment of visual acuity.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
There are a large number of patients with significant deviations, so we have to work with the analysis group per protocol, evaluable patients who meet the inclusion criteria and perform a valid follow-up.	

Primary: Efficacy at 4 weeks

End point title	Efficacy at 4 weeks
End point description:	
End point type	Primary
End point timeframe:	
To establish efficacy at 4 weeks of a single intravitreal injection of etamsylate in the improvement of visual acuity in patients diagnosed with dry or exudative DMAE.	

End point values	Treatment	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Percentage				
success	10	13		
failure	6	2		

Attachments (see zip file)	Final Report - PRELIMINARY RESULTS OF ETAMSYLATE IN

Statistical analyses

Statistical analysis title	Chi-Squared

Statistical analysis description:

The "treatment success" is defined as the improvement of the best corrected visual acuity of 1 or more letters in the ETDRS optotype in relation to the baseline value.
"Treatment failure" is defined as opposed to "treatment success" as the absence of changes in the best corrected visual acuity or the loss of 1 or more letters in the ETDRS optotype in relation to the baseline value.
Efficacy is assessed in relation to the proportion of patients who present "treatment success" in week 4.

Comparison groups	Treatment v Control
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.025
Method	Chi-squared
Parameter estimate	Proportion

Notes:

[1] - If only the superiority of etamsylate can be demonstrated by proportion of successes, the result of the study will be considered positive.

Secondary: efficacy at 16 weeks

End point title	efficacy at 16 weeks

End point description:

End point type	Secondary

End point timeframe:

Evaluate the efficacy at 16 weeks of a single intravitreal injection of etamsylate in improving visual acuity in patients diagnosed with dry or exudative AMD

End point values	Treatment	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: Percentage				
success	7	9		
failure	5	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the duration of the study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	overall study

Reporting group description: -

Serious adverse events	overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0.02 %

Non-serious adverse events	overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)		
Eye disorders			
elevated intraocular pressure	Additional description: Patient from the control group with dry AMD. He was treated with "Sanfor".		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2016	Reduction of visits
01 December 2016	change of objectives and inclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported