Clinical trial results:
Phase III comparative clinical trial to evaluate the efficacy of amniotic membrane extract for the treatment of severe dry eye disease, in comparison with autologous serum eyedrops.

Summary

EudraCT number	2011-006287-50
Trial protocol	ES
Global end of trial date	11 February 2019

Results information

Result version number	v1 (current)
This version publication date	27 August 2021
First version publication date	27 August 2021
Summary attachment (see zip file)	FINAL REPORT (SPANISH) (Informe final de resultados EMAOS 27-05-2020. FIRMADO.pdf)

Trial information

Trial identification

Sponsor protocol code	EMAOS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra
Sponsor organisation address	Avda. Pío XII, 36, Pamplona, Spain, 31008
Public contact	UCICEC, Clínica Universidad de Navarra, 34 948 255 400 2725, ucicec@unav.es
Scientific contact	UCICEC, Clínica Universidad de Navarra, 34 948 255 400 2725, ucicec@unav.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	26 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2019
Global end of trial reached?	Yes
Global end of trial date	11 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the efficacy of topical amniotic membrane extract to treat symptoms of severe dry eye disease.

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonisation (ICH) in relation to good clinical practice and related regulatory requirements. The investigator was familiar with and correctly handled the study drug as described in the protocol dossier. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki in its latest revision and with current legislation. The ethics committee reviewed all study documentation in order to protect the rights, safety and welfare of patients. The investigator provided the ethics committee with the protocol, informed consent, written information provided to patients, safety updates, annual progress reports and any amendments to these documents. The ethics committee, after review, gave its approval for the study to be carried out.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2016
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: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	11
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patient recruitment period took place from 04/12/2015 to 20/12/2018. 12 patients were recruited, 6 of whom were assigned to the control arm and 6 to the experimental treatment arm. One patient discontinued for personal reasons and another for non-drug related discomfort. A third was a screening failure.

Pre-assignment

Screening details:

Patients between 18 and 80 years old, diagnosed by severe or very severe dry eye according to Dry Eye WorkShop (DEWS) classification.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The study was conducted with a blinded evaluator. The patient was aware of the treatment, as in order to obtain the autologous serum, blood had to be drawn from the patient. In addition, the person who dispensed the eye drops to the patient was also aware of the treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm

Arm description:

Patients in this arm are treated with amniotic membrane extract.

Arm type	Experimental
Investigational medicinal product name	Amniotic membrane extract
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ophthalmic use

Dosage and administration details:

The patient will be administered 1 drop (concentration of 50 micrograms/millilitre) in both eyes 4 times a day for 12 weeks.

Arm title	Control arm

Arm description:

Patients in this arm are treated with autologous serum.

Arm type	Active comparator
Investigational medicinal product name	autologous serum
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ophthalmic use

Dosage and administration details:

The patient will be administered 1 drop 4 times a day for 12 weeks.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Because of the trial design, the patient and the investigator could not be blinded to the treatment. However, the assessor/evaluator was blinded to the treatment.

Number of subjects in period 1	Treatment Arm	Control arm
Started	6	6
Completed	5	4
Not completed	1	2
screening failure	-	1
personal problems	-	1
Discomfort not related to treatment.	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	1	1	
Gender categorical Units: Subjects			
Female	11	11	
Male	1	1	

End points

End points reporting groups

Reporting group title	Treatment Arm
Reporting group description:	
Patients in this arm are treated with amniotic membrane extract.	
Reporting group title	Control arm
Reporting group description:	
Patients in this arm are treated with autologous serum.	

Primary: Efficacy of amniotic membrane extract

End point title	Efficacy of amniotic membrane extract
End point description:	
Effectiveness is assessed by determining the tear volume and clearance by Schirmer Test type I and FCT (Fluorescein Clearance test) according to Tseng technique (10, 20 and 30 minutes), the tear stability by TBUT (tear break up time) and the ocular surface Impression cytology analysis: HLA-DR and MUC1 expression. For each of the variables per visit, the mean/median of the results obtained in the right eye and in the left eye have also been calculated and the results are indicated as "both eyes".Comparisons are made between "right eye" and "left eye". Comparisons are also made between the control and experimental branches using the variable resulting from finding the mean between the two eyes, with the data obtained in V4 and V5. No statistically significant differences were found when comparing the two treatment groups for any of the study variables.	
End point type	Primary
End point timeframe:	
Efficacy is assessed at all trial visits.	

End point values	Treatment Arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: NA				
arithmetic mean (standard deviation)				
tear volume and clearance V4	4 (± 4.73)	1.25 (± 0.65)		
tear stability by TBUT V4	1.3 (± 1.04)	3 (± 1.41)		
HLA-DR expression V4	1 (± 0.4)	3.43 (± 2.82)		
Expresión de MUC1 V4	6.65 (± 5.50)	11.1 (± 9.32)		
tear volume and clearance V5	2.1 (± 1.30)	3.63 (± 4.18)		
tear stability by TBUT V5	2.6 (± 1.30)	3.37 (± 0.48)		

Statistical analyses

Statistical analysis title	Sum of ranks Wilcoxon (U de Mann-Whitney).
Comparison groups	Treatment Arm v Control arm

Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Notes:

[1] - The results obtained in the control arm (autologous serum) versus the experimental arm (amniotic membrane extract) are compared at V4 and V5 where data were obtained for each variable explored.

Secondary: Clinical improvement

End point title	Clinical improvement

End point description:

At V4, four of the five patients who received amniotic membrane serum (80%) perceived subjective clinical improvement. With autologous serum, two patients out of 4 patients (50%) improved up to V4. The direction of these changes supports the hypothesis of a possible effect of amniotic membrane serum, as the difference in ratios at V4 indicates that the experimental treatment produces a 30% greater improvement.

End point type	Secondary

End point timeframe:

Subjective clinical improvement of trial patients is assessed at visits 2, 3 and 4.

End point values	Treatment Arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: incidence of improvement				
Clinical improvement	4	2		
No clinical improvement	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patient safety is assessed throughout their participation in the study. A final follow-up visit is made four weeks after the end of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	ND
Dictionary version	ND

Reporting groups

Reporting group title	All the patients

Reporting group description: -

Serious adverse events	All the patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All the patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)		
General disorders and administration site conditions			
vocal cord oedema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Social circumstances			
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Facial rosacea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
proctalgia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Intense pruritus on abdomen, arms and legs			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
foreign body in left hand			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
left shoulder pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

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