Clinical trial results:
A pilot study towards a therapy with prednisolone encapsulated liposomes for the treatment of Graves' Orbitopathy with reduced systemic steroid exposure

Summary

EudraCT number	2017-001158-33
Trial protocol	NL
Global end of trial date	19 December 2019

Results information

Result version number	v1
This version publication date	07 March 2020
First version publication date	07 March 2020

Trial information

Trial identification

Sponsor protocol code	OZR-2016-34

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register: NL6404

Notes:

Sponsors

Sponsor organisation name	The Rotterdam Eye Hospital
Sponsor organisation address	PO Box 70030, Rotterdam, Netherlands, 3000LM
Public contact	Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, 31 104023430, r.wubbels@oogziekenhuis.nl
Scientific contact	Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, 31 104023430, r.wubbels@oogziekenhuis.nl

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	28 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Nanocort is safe and effectively reduces the inflammatory signs and symptoms of active GO.

Protection of trial subjects:

In this study it is hypothesized that treatment of Graves' Orbitopathy with lower doses of long-circulating liposomal prednisolone (Nanocort, LCLP), instead of high doses of methylprednisolone, can be effective while the number of adverse events is reduced.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2017
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	Netherlands: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	8
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Rotterdam Eye Hospital, Netherlands, november 2017 until december 2018.

Pre-assignment

Screening details:

Moderate-to-severe Graves' orbitopathy, clinical activity score (CAS) ≥ 3.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nanocort

Arm description:

All participants received treatment.

Arm type	Experimental
Investigational medicinal product name	Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will be treated with 150 mg/infusion of Nanocort administered as an IV infusion at week 1 and 3.
Nanocort will be infused over approximately 2.5 hours.

Number of subjects in period 1	Nanocort
Started	10
Completed	7
Not completed	3
Revised diagnosis.	1
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Nanocort
Reporting group description:	
All participants received treatment.	

Reporting group values	Nanocort	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	8	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	56		
standard deviation	± 13	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	3	3	
CAS OD at baseline			
Clinical activity score (CAS) for Graves' ophthalmopathy (GO): 1 Spontaneous retrobulbar pain 2 Pain on attempted upward or downward gaze 3 Redness of eyelids 4 Redness of conjunctiva 5 Swelling of caruncle or plica 6 Swelling of eyelids 7 Swelling of conjunctiva (chemosis) (Inactive GO: CAS < 3; Active GO: CAS ≥ 3)			
Units: Ordinal scale			
arithmetic mean	4.3		
standard deviation	± 0.7	-	
CAS OS at baseline			
Clinical activity score (CAS) for Graves' ophthalmopathy (GO): 1 Spontaneous retrobulbar pain 2 Pain on attempted upward or downward gaze 3 Redness of eyelids 4 Redness of conjunctiva 5 Swelling of caruncle or plica 6 Swelling of eyelids 7 Swelling of conjunctiva (chemosis) (Inactive GO: CAS < 3; Active GO: CAS ≥ 3)			

Units: Ordinal scale			
arithmetic mean	4.5		
standard deviation	± 0.7	-	

Subject analysis sets

Subject analysis set title	CAS
Subject analysis set type	Per protocol

Subject analysis set description:
Clinical activity score

Reporting group values	CAS		
Number of subjects	10		
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	56		
standard deviation	± 13		
Gender categorical Units: Subjects			
Female Male			
CAS OD at baseline			
Clinical activity score (CAS) for Graves' ophthalmopathy (GO): 1 Spontaneous retrobulbar pain 2 Pain on attempted upward or downward gaze 3 Redness of eyelids 4 Redness of conjunctiva 5 Swelling of caruncle or plica 6 Swelling of eyelids 7 Swelling of conjunctiva (chemosis) (Inactive GO: CAS < 3; Active GO: CAS ≥ 3)			
Units: Ordinal scale			
arithmetic mean	4.3		
standard deviation	± 0.7		
CAS OS at baseline			
Clinical activity score (CAS) for Graves' ophthalmopathy (GO): 1 Spontaneous retrobulbar pain 2 Pain on attempted upward or downward gaze 3 Redness of eyelids 4 Redness of conjunctiva 5 Swelling of caruncle or plica 6 Swelling of eyelids			

7 Swelling of conjunctiva (chemosis) (Inactive GO: CAS < 3; Active GO: CAS ≥ 3)			
Units: Ordinal scale			
arithmetic mean	4.5		
standard deviation	± 0.7		

End points

End points reporting groups

Reporting group title	Nanocort
Reporting group description:	
All participants received treatment.	
Subject analysis set title	CAS
Subject analysis set type	Per protocol
Subject analysis set description:	
Clinical activity score	

Primary: Sustained response

End point title	Sustained response[1]
End point description:	
End point type	Primary
End point timeframe:	
Sustained response at 6 and 13 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary endpoint is a sustained response at weeks 6 and 13. As this is a pilot study, only the proportion of sustained responses is reported.

End point values	Nanocort			
Subject group type	Reporting group			
Number of subjects analysed	9[2]			
Units: Subjects	2			

Notes:

[2] - Patient with revised diagnosis not included.

Statistical analyses

No statistical analyses for this end point

Secondary: CAS OD at 6 weeks

End point title	CAS OD at 6 weeks
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Nanocort	CAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: CAS				
arithmetic mean (standard deviation)	4.3 (± 0.7)	1.6 (± 2.0)		

Statistical analyses

Statistical analysis title	Paired t-test (relative to baseline)
Comparison groups	Nanocort v CAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: CAS OS at 6 weeks

End point title	CAS OS at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks

End point values	Nanocort	CAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: CAS				
arithmetic mean (standard deviation)	4.5 (± 0.7)	1.4 (± 1.6)		

Statistical analyses

Statistical analysis title	Paired t-test (relative to baseline)
Comparison groups	Nanocort v CAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: CAS OD at 13 weeks

End point title	CAS OD at 13 weeks
End point description:	

End point type	Secondary
End point timeframe:	
13 weeks	

End point values	Nanocort	CAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: CAS				
arithmetic mean (standard deviation)	4.3 (± 2.0)	2.0 (± 2.2)		

Statistical analyses

Statistical analysis title	Paired t-test (relative to baseline)
Comparison groups	Nanocort v CAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: CAS OS at 13 weeks

End point title	CAS OS at 13 weeks
End point description:	

End point type	Secondary
End point timeframe:	
13 weeks	

End point values	Nanocort	CAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: CAS				
arithmetic mean (standard deviation)	4.5 (± 0.7)	0.8 (± 1.0)		

Statistical analyses

Statistical analysis title	Paired t-test (relative to baseline)
Comparison groups	Nanocort v CAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At the time of infusion, and at 13 weeks.

Adverse event reporting additional description:

Orbital allergic response.
Non-responder.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Nanocort

Reporting group description: -

Serious adverse events	Nanocort		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Ocular allergic reaction			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non responder			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Nanocort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)		
Vascular disorders			

Blood pressure increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 4 / 10 (40.00%) 4		
Eye disorders Diplopia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2018	Inclusion criteria adapted.
05 November 2018	Update IMPD due to expired IMP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported