



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 | v2 (current) |
| This version publication date | 28 January 2021 |
| First version publication date | 07 March 2020 |
| Version creation reason | • Changes to summary attachments Publication of results. |
| Summary attachment (see zip file) | Abstract (PMID 33423386) (PMID 33423386_Abstract.pdf) |

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 \geq 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: Due to the small sample size of this proof-of-concept study, no formal statistical analysis was performed.

| 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 (\pm 0.7) | 1.6 (\pm 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 (\pm 0.7) | 1.4 (\pm 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 (\pm 0.7) | 0.8 (\pm 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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33423386>