

**Clinical trial results:**

A Phase II, open-label, ophthalmological external investigator-blinded, single-center, randomized, superiority, no profit, pilot clinical trial to evaluate the effects of atorvastatin on Graves' Orbitopathy (GO) in hypercholesterolemic patients with moderate-to-severe and active GO subjected to intravenous glucocorticoid therapy: the STAGO study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-001317-33 |
| Trial protocol | IT |
| Global end of trial date | 30 April 2021 |

Results information

| | |
|-----------------------------------|-------------------------------------|
| Result version number | v1 (current) |
| This version publication date | 16 October 2022 |
| First version publication date | 16 October 2022 |
| Summary attachment (see zip file) | medical journal article (STAGO.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|-------|
| Sponsor protocol code | STAGO |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03110848 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Pisa |
| Sponsor organisation address | Via Paradisa, 2, Pisa, Italy, |
| Public contact | U.O. Endocrinologia 1, AOUP, 0039 050997346, michele.marino@med.unipi.it |
| Scientific contact | U.O. Endocrinologia 1, AOUP, 0039 050997346, michele.marino@med.unipi.it |
| Sponsor organisation name | University of Pisa |
| Sponsor organisation address | Via Paradisa 2, Pisa, Italy, |
| Public contact | Michele Marinò, University of Pisa, 0039 05997346, michele.marino@unipi.it |
| Scientific contact | Michele Marinò, University of Pisa, 0039 05997346, michele.marino@unipi.it |
| Sponsor organisation name | University of Pisa |
| Sponsor organisation address | Via Paradisa 2, Pisa, Italy, 56124 |
| Public contact | Michele Marinò, University of Pisa, 0039 0597346, michele.marino@unipi.it |
| Scientific contact | Michele Marinò, University of Pisa, 0039 05997346, michele.marino@unipi.it |

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 | 03 May 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 April 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of atorvastatin treatment on the overall outcome of Graves' Orbitopathy at 24 weeks, in hypercholesterolemic patients with Graves' disease and moderately severe, active Graves' Orbitopathy to be treated with intravenous glucocorticoids .

Protection of trial subjects:

Omeprazole 20 mg once a day for the first 12 weeks of the study alongside the intravenous methylprednisolone treatment. Omeprazole was administered to counter side-effects of the intravenous methylprednisolone regimen.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2020 |
| 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 | Italy: 88 |
| Worldwide total number of subjects | 88 |
| EEA total number of subjects | 88 |

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) | 60 |
| From 65 to 84 years | 28 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited consecutively over a 6 month period and randomly assigned (1:1) in 11 randomisation blocks of eight patients to receive methylprednisolone and atorvastatin (ST group) or methylprednisolone alone (NST group; the control group).

Pre-assignment

Screening details:

119 participants were screened for eligibility. Among them, 31 subjects were excluded according to the inclusion and exclusion criteria of the study (for more details, please see the paper attached to the trial information page of this form)

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 88 |
| Number of subjects completed | 88 |

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | baseline period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Only the ophthalmological investigator was blinded.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | methylprednisolone and atorvastatin (ST group) |

Arm description:

Patients received intravenous methylprednisolone plus atorvastatin. Intravenous methylprednisolone was administered according to a previously described protocol: 500 mg once a week for 6 weeks followed by 250 mg once a week for another 6 weeks (cumulative dose 4.5 g; appendix p 8). Atorvastatin was administered orally with a dosage of 20 mg once a day for 24 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | atorvastatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg once a day for 24 weeks

| | |
|------------------|--------------------------------|
| Arm title | methylprednisolone (NST group) |
|------------------|--------------------------------|

Arm description:

Patients received intravenous methylprednisolone, according to a previously described protocol: 500 mg once a week for 6 weeks followed by 250 mg once a week for another 6 weeks (cumulative dose 4.5 g; appendix p 8). Patients in the ST group also received 20 mg oral atorvastatin once a day for 24 weeks.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|-----------------------------------|
| Investigational medicinal product name | atorvastatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 20 mg once a day for 24 weeks | |
| Investigational medicinal product name | methylprednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for injection/infusion |
| Routes of administration | Intravenous bolus use |
| Dosage and administration details: | |
| 500 mg/week | |
| Investigational medicinal product name | methylprednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for injection/infusion |
| Routes of administration | Intravenous bolus use |
| Dosage and administration details: | |
| 500 mg/week | |

| Number of subjects in period 1 | methylprednisolone and atorvastatin (ST group) | methylprednisolone (NST group) |
|---------------------------------------|--|--------------------------------|
| Started | 44 | 44 |
| Completed | 44 | 44 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | methyprednisolone and atorvastatin (ST group) |
|-----------------------|---|

Reporting group description:

Patients received intravenous methyprednisolone plus atorvastatin. Intravenous methyprednisolone was administered according to a previously described protocol: 500 mg once a week for 6 weeks followed by 250 mg once a week for another 6 weeks (cumulative dose 4.5 g; appendix p 8). Atorvastatin was administered orally with a dosage of 20 mg once a day for 24 weeks.

| | |
|-----------------------|------------------------------|
| Reporting group title | metyprednisolone (NST group) |
|-----------------------|------------------------------|

Reporting group description:

Patients received intravenous methyprednisolone, according to a previously described protocol: 500 mg once a week for 6 weeks followed by 250 mg once a week for another 6 weeks (cumulative dose 4.5 g; appendix p 8). Patients in the ST group also received 20 mg oral atorvastatin once a day for 24 weeks.

| Reporting group values | methyprednisolone and atorvastatin (ST group) | metyprednisolone (NST group) | Total |
|---------------------------------------|---|------------------------------|-------|
| Number of subjects | 44 | 44 | 88 |
| Age categorical Units: Subjects | | | |
| Adults (18-75 years) | 44 | 44 | 88 |
| Age continuous Units: years | | | |
| arithmetic mean | 55.3 | 52.4 | |
| standard deviation | ± 9.2 | ± 11.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 32 | 29 | 61 |
| Male | 12 | 15 | 27 |

Subject analysis sets

| | |
|----------------------------|----------------|
| Subject analysis set title | ITT population |
|----------------------------|----------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All the subjects who completed at least the 12-week visit.

| Reporting group values | ITT population | | |
|---------------------------------------|----------------|--|--|
| Number of subjects | 80 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-75 years) | 80 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | ± | | |
| Gender categorical Units: Subjects | | | |
| Female | | | |
| Male | | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | methylprednisolone and atorvastatin (ST group) |
| Reporting group description: Patients received intravenous methylprednisolone plus atorvastatin. Intravenous methylprednisolone was administered according to a previously described protocol: 500 mg once a week for 6 weeks followed by 250 mg once a week for another 6 weeks (cumulative dose 4·5 g; appendix p 8). Atorvastatin was administered orally with a dosage of 20 mg once a day for 24 weeks. | |
| Reporting group title | methylprednisolone (NST group) |
| Reporting group description: Patients received intravenous methylprednisolone, according to a previously described protocol: 500 mg once a week for 6 weeks followed by 250 mg once a week for another 6 weeks (cumulative dose 4·5 g; appendix p 8). Patients in the ST group also received 20 mg oral atorvastatin once a day for 24 weeks. | |
| Subject analysis set title | ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All the subjects who completed at least the 12-week visit. | |

Primary: overall outcome of Graves' orbitopathy

| | |
|----------------------------------|--|
| End point title | overall outcome of Graves' orbitopathy |
| End point description: | |
| End point type | Primary |
| End point timeframe: 24 weeks | |

| End point values | methylprednisolone and atorvastatin (ST group) | methylprednisolone (NST group) | | |
|-----------------------------|--|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 39 | | |
| Units: 21/41 | | | | |
| responders | 21 | 11 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | fisher exact test |
| Comparison groups | methylprednisolone and atorvastatin (ST group) v methylprednisolone (NST group) |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Fisher exact |
| Parameter estimate | AR |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Follow up period

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | ST group |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|-----------|
| Reporting group title | NST group |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events | ST group | NST group | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 44 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | ST group | NST group | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 44 (27.27%) | 14 / 44 (31.82%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 44 (2.27%) | |
| occurrences (all) | 1 | 1 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 44 (2.27%) | |
| occurrences (all) | 1 | 1 | |
| face swelling | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 44 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| palpitations subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 2 / 44 (4.55%) 2 | |
| Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 44 (2.27%) 1 | |
| Gastritis subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 44 (2.27%) 1 | |
| abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 44 (0.00%) 0 | |
| Hepatobiliary disorders liver enzymes increasing subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 44 (2.27%) 1 | |
| Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 44 (0.00%) 0 | |
| rush subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 44 (2.27%) 1 | |
| Psychiatric disorders sleeping disorders subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 44 (2.27%) 1 | |
| depressive mood subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 44 (2.27%) 1 | |
| Musculoskeletal and connective tissue disorders Myositis subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 44 (0.00%) 0 | |
| Infections and infestations | | | |

| | | | |
|------------------------------------|----------------|----------------|--|
| Cystitis | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 44 (2.27%) | |
| occurrences (all) | 2 | 1 | |
| Oral fungal infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 44 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 44 (2.27%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 44 (2.27%) | |
| occurrences (all) | 1 | 1 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 44 (2.27%) | |
| occurrences (all) | 0 | 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