

**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	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.

Reporting group values	methylprednisolone and atorvastatin (ST group)	methylprednisolone (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