Clinical trial results:
Mycophenolate sodium in Graves' orbitopathy

Summary

EudraCT number	2008-002123-93
Trial protocol	DE
Global end of trial date	10 May 2017

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020
Summary attachment (see zip file)	Lancet Diabetes Endocrinol 2018 (2018_MINGO-PIIS2213-8587(18)30020-2 (1).pdf)

Trial information

Trial identification

Sponsor protocol code	MINGO

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Medical Center Mainz
Sponsor organisation address	Langenbeckstreet 1, Mainz, Germany,
Public contact	Professor George J. Kahaly, University Medical Center Mainz, george.kahaly@unimedizin-mainz.de
Scientific contact	Professor George J. Kahaly, University Medical Center Mainz, george.kahaly@unimedizin-mainz.de
Sponsor organisation name	University Medical Center Mainz
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Scientific contact	George J. Kahaly University Medical Center Mainz Langenbeckstreet 1 55131 Mainz, George J. Kahaly University Medical Center Mainz Langenbeckstreet 1 55131 Mainz, george.kahaly@unimedizin-mainz.de

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	07 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2017
Global end of trial reached?	Yes
Global end of trial date	10 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Response rate at week 12: comparison of the combination treatment vs. steroid monotherapy
- Relapse rate at weeks 24 and 36 in both groups

Protection of trial subjects:

All patients underwent complete ophthalmic and endocrine assessment at baseline and 6, 12, 24, and 36 weeks after starting treatment. Secondary Endpoint was safety of the combination treatment Mycophenolate Sodium + Methylprednisolone i.v. Adverse events were documented and coded in accordance with the standardised medical dictionary for regulatory affairs (MedDRA),17–19 as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2009
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	Germany: 137
Country: Number of subjects enrolled	Italy: 27
Worldwide total number of subjects	164
EEA total number of subjects	164

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)	153
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Baseline assessments (general medical history, laboratory tests, endocrine and ophthalmic investigations, physical examination, vital signs, subjective assessments) may also be performed up to 2 weeks before baseline (Screening period). Results must be available and negative prior to administration of medication.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Data analyst, Investigator[2]

Blinding implementation details:

All ophthalmologists and the Johannes Gutenberg University expert statistician were masked to group assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Methylprednisolone Monotherapy

Arm description:

During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week
for 6 weeks with a cumulative dose of 4·5 g.

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week for 6 weeks with a cumulative dose of 4·5 g.

Arm title	Methylprednisolone and Mycophenolate Sodium

Arm description:

During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week
for 6 weeks with a cumulative dose of 4·5 g. In addition to the methylprednisolone, patients in the combination methylprednisolone and mycophenolate group also received 360 mg of mycophenolate orally twice per day for 24 weeks with a cumulative mycophenolate dose of 120 g.

Arm type	Experimental
Investigational medicinal product name	Mycophenolate Sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week
for 6 weeks with a cumulative dose of 4·5 g. In addition to the methylprednisolone, patients in the combination methylprednisolone and mycophenolate group also received 360 mg of mycophenolate

orally twice per day for 24 weeks with a cumulative mycophenolate dose of 120 g.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The trial was observer-masked. Only Opththalmologists and the statistician were blinded to treatment allocation.

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

Justification: The trial was observer-masked. Only Opththalmologists and the statistician were blinded to treatment allocation.

Number of subjects in period 1	Methylprednisolone Monotherapy	Methylprednisolone and Mycophenolate Sodium
Started	81	83
Completed	81	83

Baseline characteristics

End points

End points reporting groups

Reporting group title	Methylprednisolone Monotherapy
Reporting group description:	
During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week for 6 weeks with a cumulative dose of 4·5 g.	
Reporting group title	Methylprednisolone and Mycophenolate Sodium
Reporting group description:	
During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week for 6 weeks with a cumulative dose of 4·5 g. In addition to the methylprednisolone, patients in the combination methylprednisolone and mycophenolate group also received 360 mg of mycophenolate orally twice per day for 24 weeks with a cumulative mycophenolate dose of 120 g.	

Primary: Response rate at week 12: comparison of the combination treatment vs. steroid

End point title	Response rate at week 12: comparison of the combination treatment vs. steroid
End point description:	
End point type	Primary
End point timeframe:	
Baseline to week 12	

End point values	Methylprednisolone Monotherapy	Methylprednisolone and Mycophenolate Sodium		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	76		
Units: patients	36	48		

Statistical analyses

Statistical analysis title	Primary outcome
Comparison groups	Methylprednisolone Monotherapy v Methylprednisolone and Mycophenolate Sodium
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Fisher exact

Notes:
[1] - Comparison

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From Baseline to visit 36 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Safety Analysis

Reporting group description:

from baseline to visit 36 weeks

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Frequency threshold for reporting non-serious adverse Events was set at 5%. No AE occurred in more than 3 patients; a detailed safety analysis is given in the attached manuscript.

Serious adverse events	Safety Analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 164 (14.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituritary gland neoplasm			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
trauma			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Thyroidectomy			
subjects affected / exposed	3 / 164 (1.83%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
appendectomy			

subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Optic neuropathy			
subjects affected / exposed	12 / 164 (7.32%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
hallux rigidus			

subjects affected / exposed	1 / 164 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 164 (0.00%)		

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