



## 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,<br>george.kahaly@unimedizin-mainz.de                                                                                                                     |
| Scientific contact           | Professor George J. Kahaly, University Medical Center Mainz,<br>george.kahaly@unimedizin-mainz.de                                                                                                                     |
| Sponsor organisation name    | University Medical Center Mainz                                                                                                                                                                                       |
| Sponsor organisation address | Langenbeckstreet 1, Mainz, Germany,                                                                                                                                                                                   |
| Public contact               | George J. Kahaly<br>University Medical Center Mainz<br>Langenbeckstreet 1<br>55131 Mainz, George J. Kahaly<br>University Medical Center Mainz<br>Langenbeckstreet 1<br>55131 Mainz, george.kahaly@unimedizin-mainz.de |
| Scientific contact           | George J. Kahaly<br>University Medical Center Mainz<br>Langenbeckstreet 1<br>55131 Mainz, George J. Kahaly<br>University Medical Center Mainz<br>Langenbeckstreet 1<br>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 <sup>[1]</sup>               |
| Roles blinded                | Data analyst, Investigator <sup>[2]</sup> |

Blinding implementation details:

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

### Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | 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.

|                  |                                             |
|------------------|---------------------------------------------|
| <b>Arm title</b> | 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 Ophthalmologists 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 Ophthalmologists and the statistician were blinded to treatment allocation.

| Number of subjects in period 1 | Methylprednisolone<br>Monotherapy | Methylprednisolone<br>and Mycophenolate<br>Sodium |
|--------------------------------|-----------------------------------|---------------------------------------------------|
|                                |                                   |                                                   |
| Started                        | 81                                | 83                                                |
| Completed                      | 81                                | 83                                                |

## Baseline characteristics

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Methylprednisolone Monotherapy              |
| Reporting group description:<br>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:<br>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:<br>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 <sup>[1]</sup>                                                         |
| P-value                                 | < 0.05                                                                       |
| Method                                  | Fisher exact                                                                 |

---

Notes:

[1] - Comparison



## Adverse events

### Adverse events information<sup>[1]</sup>

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) |                   |  |  |
| Pituitary 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 %

|                                                       |                 |  |  |
|-------------------------------------------------------|-----------------|--|--|
| <b>Non-serious adverse events</b>                     | 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