# Clinical trial results:
# Efficacy and safety of a human normal immunoglobulin product for intravenous administration (IVIg) in the treatment of dermatomyositis (DM) and polymyositis (PM): prospective, randomised, double-blind, placebo-controlled study

## Summary

| | |
|---|---|
| EudraCT number | 2005-002463-88 |
| Trial protocol | DE AT IT HU CZ |
| Global end of trial date | 06 September 2011 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 August 2016 |
| First version publication date | 08 August 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | L00133 IV 301 (ORF) |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | ISRCTN87782942 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Orfagen |
| Sponsor organisation address | 3, avenue Hubert Curien, Toulouse CEDEX 1, France, 31035 |
| Public contact | Clinical project manager, Orfagen, info@orfagen.com |
| Scientific contact | Clinical project manager, Orfagen, info@orfagen.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000415-PIP01-08 |
| 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 July 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 June 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 September 2011 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of the IVIg product as adjunctive treatment to conventional glucocorticosteroids (GS) and immunosuppressors (IS) in dermatomyositis (DM) and polymyositis (PM) patients with insufficient improvement of muscle strength.

Protection of trial subjects:

At baseline, according to the "note for guidance on the clinical investigation of human normal immunoglobulin for intravenous administration" (CPMP/BPWG/388/95 rev.1), a pre-treatment serum sample was performed and stored at – 70°C until the sponsor allows its destruction (after clinical study report edition), for possible testing.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 October 2006 |
| 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 | Austria: 5 |
| Country: Number of subjects enrolled | Czech Republic: 12 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | Italy: 5 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 44 |

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) | 37 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A run-in period (observational period where patients received conventional therapies) aimed at ensuring that patients entered the randomised, active part of the study, only if they insufficiently improve their muscle strength under those conventional therapies.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 67[1] |
| Number of subjects completed | 44 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Adverse event, non-fatal: 6 |
| Reason: Number of subjects | Inclusion period closed: 4 |
| Reason: Number of subjects | Not enrollable in the following study period: 9 |
| Reason: Number of subjects | Consent withdrawn by subject: 2 |
| Reason: Number of subjects | Concomitant disease: 1 |
| Reason: Number of subjects | Wrong diagnosis: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Subjects started a pre-assignement period that aimed at ensuring that patients entered the randomised, active part of the study only if they insufficiently improve their muscle strength under conventional thérapies. Enrolled subjects are defined as subjects who received at least once one of the study treatment

### Period 1

| | |
|---|---|
| Period 1 title | Study Period I |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Carer, Subject, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | L0133 Group |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | L0133 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

2g/Kg (40 ml/Kg) per month, delivered in 2 consecutive days (1g/Kg daily or 20 ml/Kg daily).
Test product had to be infused intravenously at an initial rate of 0.46 – 0.92 mL/Kg/hr (10 –20 drops per minute) for 20 – 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 1.85 mL/Kg/hr (40 drops / minute) for the remainder of the infusion. The entire time necessary to infuse 40 mL/Kg daily (or 1 mg/Kg daily of IVIg product) is about 11h (30 minutes at the rate of 0.46 – 0.92 mL/Kg/hr and about 10h30 at the rate of 1.85 mL/Kg/hr).

Patients with abnormal renal parameters, history of myocardial and stroke and with blood viscosity abnormalities received the test product over 5 consecutive days (0.4 g/Kg daily or 8 ml/Kg daily).

| **Arm title** | Placebo Group |
|---|---|
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo (NaCl 9‰)
40ml/Kg per month, delivered in 2 consecutive days (20mL/Kg daily). Patients with abnormal renal parameters, history of myocardial and stroke and with blood viscosity abnormalities will receive the test product during 5 consecutive days (8mL/Kg daily).

| **Number of subjects in period 1** | L0133 Group | Placebo Group |
|---|---|---|
| Started | 22 | 22 |
| Completed | 21 | 22 |
| Not completed | 1 | 0 |
| Adverse event, serious fatal | 1 | - |

## Period 2

| Period 2 title | Study period II |
|---|---|
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | L0133 / L0133 Group |

Arm description:

Patients having received 6 months of active treatment (3 months of Period I, followed by 3 months of Period II)

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | L0133 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

2g/Kg (40 ml/Kg) per month, delivered in 2 consecutive days (1g/Kg daily or 20 ml/Kg daily).
Test product had to be infused intravenously at an initial rate of 0.46 – 0.92 mL/Kg/hr (10 –20 drops per minute) for 20 – 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 1.85 mL/Kg/hr (40 drops / minute) for the remainder of the infusion. The entire time necessary to infuse 40 mL/Kg daily (or 1 mg/Kg daily of IVIg product) is about 11h (30 minutes at the rate of 0.46 – 0.92 mL/Kg/hr and about 10h30 at the rate of 1.85 mL/Kg/hr).
Patients with abnormal renal parameters, history of myocardial and stroke and with blood viscosity abnormalities received the test product over 5 consecutive days (0.4 g/Kg daily or 8 ml/Kg daily).

| **Arm title** | L0133 / Placebo Group |
|---|---|

Arm description:

Patients having received 3 months of active treatment [Placebo during Period I (3months), followed by active during Period II (3 months)].

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | L0133 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

2g/Kg (40 ml/Kg) per month, delivered in 2 consecutive days (1g/Kg daily or 20 ml/Kg daily).
Test product had to be infused intravenously at an initial rate of 0.46 – 0.92 mL/Kg/hr (10 –20 drops per minute) for 20 – 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 1.85 mL/Kg/hr (40 drops / minute) for the remainder of the infusion. The entire time necessary to infuse 40 mL/Kg daily (or 1 mg/Kg daily of IVIg product) is about 11h (30 minutes at the rate of 0.46 – 0.92 mL/Kg/hr and about 10h30 at the rate of 1.85 mL/Kg/hr).
Patients with abnormal renal parameters, history of myocardial and stroke and with blood viscosity abnormalities received the test product over 5 consecutive days (0.4 g/Kg daily or 8 ml/Kg daily).

| **Number of subjects in period 2** | L0133 / L0133 Group | L0133 / Placebo Group |
|---|---|---|
| Started | 21 | 22 |
| Completed | 21 | 22 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | L0133 Group |
| Reporting group description: - | |
| Reporting group title | Placebo Group |
| Reporting group description: - | |

| Reporting group values | L0133 Group | Placebo Group | Total |
|---|---|---|---|
| Number of subjects | 22 | 22 | 44 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 18 | 19 | 37 |
| From 65-84 years | 4 | 3 | 7 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 15 | 15 | 30 |
| Male | 7 | 7 | 14 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | L0133 Group |
| Reporting group description: - | |
| Reporting group title | Placebo Group |
| Reporting group description: - | |
| Reporting group title | L0133 / L0133 Group |
| Reporting group description: | |
| Patients having received 6 months of active treatment (3 months of Period I, followed by 3 months of Period II) | |
| Reporting group title | L0133 / Placebo Group |
| Reporting group description: | |
| Patients having received 3 months of active treatment [Placebo during Period I (3months), followed by active during Period II (3 months)]. | |

### Primary: Treatment Response

| | |
|---|---|
| End point title | Treatment Response |
| End point description: | |
| Muscle strength intensity: as defined by the modified BMRC index which assigns the grades 0 to 11 to indicate the level of muscle power in 8 muscle groups (neck flexors, trapezius, deltoid, biceps, psoas, maximus and medius gluteus, and quadriceps).<br>Treatment response was defined as an improvement from baseline of BMRC score at the end of Period I as follows:<br>- Patients with baseline BMRC score between 24 and 40 included: at least 18 points improvement,<br>- Patients with baseline BMRC score between 40.5 and 56 included: at least 12 points improvement,<br>- Patients with baseline BMRC score between 56.5 and 72 included: at least 8 points improvement,<br>Patients prematurely switched from Period I to Period II due to BMRC index aggravation were considered as non-responders. | |
| End point type | Primary |
| End point timeframe: | |
| End of Period I, i.e. 84 days or earlier in case of significant deterioration of the muscle strength. | |

| **End point values** | L0133 Group | Placebo Group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: Patients | 8 | 6 | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Treatment response at the end of Period I |
| Comparison groups | L0133 Group v Placebo Group |

| | |
|---|---|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5174 |
| Method | Chi-squared |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From randomisation to study end | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Period I - L0133 Group |
| Reporting group description: - | |
| Reporting group title | Period I - Placebo Group |
| Reporting group description: - | |
| Reporting group title | Period II - L0133 / L0133 Group |
| Reporting group description: - | |
| Reporting group title | Period II - L0133 / Placebo Group |
| Reporting group description: - | |

| Serious adverse events | Period I - L0133 Group | Period I - Placebo Group | Period II - L0133 / L0133 Group |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Period II - L0133 / Placebo Group | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| **Non-serious adverse events** | Period I - L0133 Group | Period I - Placebo Group | Period II - L0133 / L0133 Group |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 22 (68.18%) | 12 / 22 (54.55%) | 11 / 21 (52.38%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Hypertension | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 1 |
| Face oedema | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Injury, poisoning and procedural complications | | | |
| Injury | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Accident | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Congenital, familial and genetic disorders | | | |
| Congenital anomaly | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Essential tremor | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 5 / 22 (22.73%) | 2 / 22 (9.09%) | 1 / 21 (4.76%) |
| occurrences (all) | 6 | 4 | 1 |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cataract | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Glaucoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 0 |
| Purpura | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin ulcer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Urge incontinence | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Adrenal disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 3 | 0 | 1 |

| | | | |
|---|---|---|---|
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| **Non-serious adverse events** | Period II - L0133 / Placebo Group | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 22 (63.64%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombophlebitis superficial | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | | |
| Injury, poisoning and procedural complications<br>Injury<br>subjects affected / exposed<br>occurrences (all)<br><br>Sternal fracture<br>subjects affected / exposed<br>occurrences (all)<br><br>Accident<br>subjects affected / exposed<br>occurrences (all)<br><br>Limb injury<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0 | | |
| Congenital, familial and genetic disorders<br>Congenital anomaly<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 22 (4.55%)<br>1 | | |
| Cardiac disorders<br>Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0 | | |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Essential tremor<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Tremor<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0 | | |

| | | | |
|---|---|---|---|
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 5 / 22 (22.73%) | | |
| occurrences (all) | 8 | | |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Purpura | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Urge incontinence<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | | |
| Endocrine disorders<br>Cushing's syndrome<br>subjects affected / exposed<br>occurrences (all)<br><br>Adrenal disorder<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0<br><br><br>1 / 22 (4.55%)<br>1 | | |
| Musculoskeletal and connective tissue disorders<br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)<br><br>Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Osteonecrosis<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0 | | |
| Infections and infestations<br>Herpes zoster<br>subjects affected / exposed<br>occurrences (all)<br><br>Meningitis aseptic<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchitis<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0<br><br><br>1 / 22 (4.55%)<br>2<br><br><br>0 / 22 (0.00%)<br>0 | | |

| | | | |
|---|---|---|---|
| Gastroenteritis viral<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Viral infection<br>subjects affected / exposed<br>occurrences (all) | <br>1 / 22 (4.55%)<br>1<br><br><br>1 / 22 (4.55%)<br>1<br><br><br>1 / 22 (4.55%)<br>1<br><br><br>0 / 22 (0.00%)<br>0 | | |
| Metabolism and nutrition disorders<br>Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 22 (0.00%)<br>0<br><br><br>0 / 22 (0.00%)<br>0 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 14 February 2006 | Clarification / modifications of the study protocol following local Ethics Committeees assessment and National Authorities assessment. |
| 22 December 2006 | Modification in the pre-assignment Period. Changes in MTX dosage |
| 11 September 2007 | Modifications in the pre-assignement period. Extension of the Study period |
| 06 May 2008 | Co-investigators' changes in 4 centers. Addition of 2 centers. |
| 27 October 2008 | Modifications in the pre-assignement period. New study protocol template. Helsinki declaration update. Extension of the study period. |
| 06 May 2010 | Extension of study period |
| 06 January 2011 | Change of sponsor address |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported