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 Units: Subjects			
Adults (18-64 years)	18	19	37
From 65-84 years	4	3	7
Gender categorical 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). Treatment response was defined as an improvement from baseline of BMRC score at the end of Period I as follows: - Patients with baseline BMRC score between 24 and 40 included: at least 18 points improvement, - Patients with baseline BMRC score between 40.5 and 56 included: at least 12 points improvement, - Patients with baseline BMRC score between 56.5 and 72 included: at least 8 points improvement, 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 occurrences (all)	0 / 22 (0.00%) 0		
Injury, poisoning and procedural complications Injury subjects affected / exposed occurrences (all) Sternal fracture subjects affected / exposed occurrences (all) Accident subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0		
Congenital, familial and genetic disorders Congenital anomaly subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1		
Cardiac disorders Tachyarrhythmia subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Essential tremor subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 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 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences (all) Adrenal disorder subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0 1 / 22 (4.55%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Osteonecrosis subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0		
Infections and infestations Herpes zoster subjects affected / exposed occurrences (all) Meningitis aseptic subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 1 / 22 (4.55%) 2 0 / 22 (0.00%) 0		

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