Clinical trial results:
A randomised, multi-centre, double-blind, active-controlled, parallel group study to assess the efficacy and safety of modified release prednisone (Lodotra®) compared to immediate release prednisone (prednisone IR) in subjects suffering from polymyalgia rheumatica (PMR).

Summary

EudraCT number	2011-002353-57
Trial protocol	DE CZ GB HU ES DK IT
Global end of trial date	25 March 2014

Results information

Result version number	v2
This version publication date	20 February 2016
First version publication date	07 August 2015
Version creation reason	• Changes to summary attachments Summary attachment is not required.

Trial information

Trial identification

Sponsor protocol code	LOD3501

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Ltd
Sponsor organisation address	Cambridge Science Park, Cambridge, United Kingdom, CB4 0GW
Public contact	European Medical Operations, Mundipharma Research Ltd, 44 1223 424900, info@contact-clinical-trials.com
Scientific contact	European Medical Operations, Mundipharma Research Ltd, 44 1223 424900, info@contact-clinical-trials.com

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	25 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2014
Global end of trial reached?	Yes
Global end of trial date	25 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To show that treatment with Lodotra® (starting dose of 15 mg daily), administered in the evening, is non-inferior to treatment with prednisone IR (starting dose of 15 mg daily), administered in the morning, with regards to the percentage of complete responders to treatment 4 weeks after randomisation.

Protection of trial subjects:

All subjects were provided with oral and written information describing the nature and duration of the study, its purpose, the procedures to be performed, the potential risks and benefits involved, and any potential discomfort. Each subject was given a copy of the Patient Information Sheet (PIS) and Informed Consent Form (ICF). The subject was asked to sign and date an ICF prior to any study-specific procedures being performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2012
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	Poland: 8
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	62
EEA total number of subjects	62

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	16
From 65 to 84 years	45
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

124 Subjects were enrolled into the study across 41 sites in 9 countries (Germany (11 sites) Czech Republic (six sites), Spain (six sites), Poland (five sites), Hungary (five sites), United Kingdom (four sites), Denmark (two sites), Romania (one site) and Italy (one site)) between 20 March 2013 and 25 March 2014.

Pre-assignment

Screening details:

124 subjects provided written informed consent, were enrolled and screened. 62 subjects failed screening therefore 62 subjects were randomised into the study. The most common reasons for screen failure were 'Failed screening procedure' (34 subjects) and 'Subject did not meet randomisation criteria' (26 subjects).

Period 1

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

Blinding implementation details:

The subject and all personnel involved with the conduct and interpretation of the study (Investigators, site personnel, and the Sponsor's staff), were blinded to the medication codes. The randomisation schedule was filed securely, such that blinding was properly maintained throughout the study. Medication codes of the double-blind were not available until all subjects completed the double-blind phase of the study and until after final data review (clinical database lock) of the core phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	Prednisone

Arm description:

Prednisone (immediate-release tablets) 15 mg daily dose administered orally in the morning and placebo Lodotra(R) administered in the evening, both with a light meal.

Arm type	Active comparator
Investigational medicinal product name	Prednisone IR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg daily dose, administered orally.

Investigational medicinal product name	placebo Lodotra(R)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

oral administration with a light meal in the evening.

Arm title	Lodotra(R)

Arm description:

Lodotra(R) tablets (modified-release) 15 mg daily dose administered in the evening and placebo prednisone tablets administered in the morning, both administered with a light meal.

Arm type	Experimental

Investigational medicinal product name	Lodotra(R)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg daily, administered orally.

Investigational medicinal product name	Placebo prednisone IR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

oral administration with a light meal in the morning.

Number of subjects in period 1	Prednisone	Lodotra(R)
Started	30	32
Completed	23	27
Not completed	7	5
Consent withdrawn by subject	2	1
Administrative	-	2
Adverse event, non-fatal	2	1
Lack of efficacy	3	1

Period 2

Period 2 title	Open-Label period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open-label period therefore no blinding was implemented.

Arms

Arm title	Open-Label

Arm description:

Lodotra(R) (modified-release) at a starting dose of 12 mg daily or prednisone (immediate-release) at a starting dose of 12 mg daily.

Arm type	Open-Label
Investigational medicinal product name	Lodotra(R)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose of 12 mg daily, administered orally.

Investigational medicinal product name	Prednisone IR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose of 12 mg daily, administered orally.

Number of subjects in period 2[1]	Open-Label
Started	27
Completed	27

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects had to fulfill criteria for entry into the open-label period (re-randomisation) and not all subjects completing the double blind-period fulfilled the criteria or wished to enter the open-label period, therefore the number of subjects completing the double blind-period is more than the number entering the open-label period.

Baseline characteristics

Reporting groups

Reporting group title	Double-Blind Period

Reporting group description: -

Reporting group values	Double-Blind Period	Total	
Number of subjects	62	62	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	45	45	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	69.4		
standard deviation	± 7.45	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	41	41	

Subject analysis sets

Subject analysis set title	Randomised population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects

Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised subjects who received at least one dose of double-blind core phase study medication

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All Full Analysis population subjects without major protocol violations. Major protocol violations were agreed at the determination of subject evaluability meeting prior to unblinding.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least one dose of study medication.

Reporting group values	Randomised population	Full Analysis Population	Per Protocol Population
Number of subjects	62	62	48
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	16	16	12
From 65-84 years	45	45	35
85 years and over	1	1	1
Age continuous			
Units: years			
arithmetic mean	69.4	69.4	69.6
standard deviation	± 7.45	± 7.45	± 7.31
Gender categorical			
Units: Subjects			
Female			
Male			

Reporting group values	Safety Population		
Number of subjects	62		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	16		
From 65-84 years	45		
85 years and over	1		
Age continuous			
Units: years			
arithmetic mean	69.4		
standard deviation	± 7.45		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Prednisone
Reporting group description:	
Prednisone (immediate-release tablets) 15 mg daily dose administered orally in the morning and placebo Lodotra(R) administered in the evening, both with a light meal.	
Reporting group title	Lodotra(R)
Reporting group description:	
Lodotra(R) tablets (modified-release) 15 mg daily dose administered in the evening and placebo prednisone tablets administered in the morning, both administered with a light meal.	
Reporting group title	Open-Label
Reporting group description:	
Lodotra(R) (modified-release) at a starting dose of 12 mg daily or prednisone (immediate-release) at a starting dose of 12 mg daily.	
Subject analysis set title	Randomised population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised subjects	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects who received at least one dose of double-blind core phase study medication	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
All Full Analysis population subjects without major protocol violations. Major protocol violations were agreed at the determination of subject evaluability meeting prior to unblinding.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of study medication.	

Primary: Percentage of complete responders at the end of the double-blind period.

End point title	Percentage of complete responders at the end of the double-blind period.
End point description:	
The percentage of complete responders (CR) at the end of the 4-week double-blind period comparing Lodotra(R) with prednisone IR. CR was defined as all three of the following: 1. ≥ 70% improvement in PMR visual analogue scale (VAS) 2. ≥ 70% reduction in the duration of morning stiffness (MST) 3. ≥ 70% reduction in C-Reactive Protein (CRP) value or CRP value < 2 times Upper Limit of Normal (ULN) The primary analysis was performed on the Per Protocol (PP) population.	
End point type	Primary
End point timeframe:	
4-week double-blind period.	

End point values	Prednisone	Lodotra(R)	Full Analysis Population	Per Protocol Population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	26[1]	22[2]	62	48
Units: percentage	14	9	27	23

Notes:

[1] - Per Protocol Population

[2] - Per Protocol Population

Statistical analyses

Statistical analysis title	Lodotra(R) is non-inferior to prednisone IR wrt CR

Statistical analysis description:

The primary endpoint was the percentage of complete responders at the end of the 4-week double-blind core phase, comparing Lodotra(R) with Prednisone IR. The comparison was used to test, in a confirmatory manner, the hypothesis that Lodotra(R) is non-inferior to Prednisone IR with respect to the percentage of complete responders at Week 4 of the double-blind core phase.

Comparison groups	Prednisone v Lodotra(R)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted Difference in proportions
Point estimate	12.22
Confidence interval	
level	95 %
sides	1-sided
lower limit	-15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the point at which the Informed Consent was signed until 7-10 days after the subject left the study. This included new AEs that were reported in the 7-10 days following the subject's completion/discontinuation visit

Adverse event reporting additional description:

Any AE that was still ongoing 7-10 days after the completion/discontinuation visit had an outcome of 'ongoing' in the CRF.
SAEs were followed until the event resolved or the event or sequelae stabilised. A treatment-emergent AE was any AE with an onset date on or after the first dose of study medication, or that worsened after the first dose.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Lodotra(R)
Reporting group description: -	
Reporting group title	Prednisone IR

Reporting group description: -

Serious adverse events	Lodotra(R)	Prednisone IR	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Temporal arteritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lodotra(R)	Prednisone IR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)	9 / 30 (30.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2013	Protocol amendment 2 (30 January 2013) was a global amendment that reflected the change in the duration of morning stiffness, indicating that patients can be classified as having PMR to >45 minutes according to the 2012 Provisional Classification Criteria for PMR (Dasgupta et al., 2012). The amendment also required the measurement of Rheumatoid Factor and Anti-Citrullinated Protein Antibodies. Elevated results for these tests indicated that a subject had underlying RA. Underlying RA would have excluded the subject from the Per Protocol population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported