Clinical trial results:
A Phase III, Randomized, Double-Blind, Double Dummy, Active Controlled, Multi-Center Study To Evaluate The Efficacy And Safety Of Intravenous Pegylated Liposomal Prednisolone Sodium Phosphate (Nanocort) Compared With Intramuscular Injection Of Methylprednisolone Acetate In Subjects With Active Rheumatoid Arthritis

Summary

EudraCT number	2015-002924-17
Trial protocol	NL BE
Global end of trial date	13 June 2018

Results information

Result version number	v1 (current)
This version publication date	18 May 2019
First version publication date	18 May 2019

Trial information

Trial identification

Sponsor protocol code	CLR_15_05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02534896
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sun Pharma Global FZE
Sponsor organisation address	Office number 43 Bloc-Y, SAIF Zone, Sharjah, United Arab Emirates, 122304
Public contact	Head-Clinical Development, Sun Pharma Advanced Research Company Limited, clinical.trials@sparcmail.com
Scientific contact	Head-Clinical Development, Sun Pharma Advanced Research Company Limited, clinical.trials@sparcmail.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	30 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2018
Global end of trial reached?	Yes
Global end of trial date	13 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy and safety (treatment of signs and symptoms) of Nanocort in subjects with active rheumatoid arthritis who are experiencing a flare/exacerbation in comparison to a standard of care medication (Depo-Medrol).

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with International Council for Harmonisation (ICH) guidance, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, the European Clinical Trial Directive 2001/20/EC of 4 Apr 2001 and European ClinicalTrial Directive 2005/28/EC of 8 Apr 2005 and local ethical and legal requirements.

Concomitant therapies taken for the long-term treatment of pre-existing conditions (as per Investigator's opinion) could be continued during the study. However, these needed to be stabilized prior to entry and continued wherever practical without variation of dose or regimen during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2016
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	Netherlands: 120
Country: Number of subjects enrolled	Belgium: 30
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	150
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 150 subjects were randomized in the study in 3 treatment groups.

Period 1

Period 1 title	Period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Treatment I
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use, Intravenous use

Dosage and administration details:

Day 1 and 15

Arm title	Arm 2

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Treatment II
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use, Intravenous use

Dosage and administration details:

Day 1 and 15 up to 12 weeks

Arm title	Arm 3

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Treatment III
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use, Intravenous use

Dosage and administration details:

Day 1 and 15

Number of subjects in period 1	Arm 1	Arm 2	Arm 3
Started	49	52	49
Completed	45	51	48
Not completed	4	1	1
Adverse event, non-fatal	2	1	1
insufficient therapeutic resonse	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description: -	
Reporting group title	Arm 2
Reporting group description: -	
Reporting group title	Arm 3
Reporting group description: -	

Reporting group values	Arm 1	Arm 2	Arm 3
Number of subjects	49	52	49
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)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	55.3	56.4	56.7
standard deviation	± 13.79	± 10.74	± 11.18
Gender categorical Units: Subjects			
Female	38	42	35
Male	11	10	14

Reporting group values	Total		
Number of subjects	150		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	115		
Male	35		

End points

End points reporting groups	
Reporting group title	Arm 1
Reporting group description: -	
Reporting group title	Arm 2
Reporting group description: -	
Reporting group title	Arm 3
Reporting group description: -	

Primary: Good/Moderate European League Against Rheumatism Responders	
End point title	Good/Moderate European League Against Rheumatism Responders
End point description:	
End point type	Primary
End point timeframe:	
Day 8	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	52	49	
Units: number of subjects				
number (not applicable)	42	45	32	

Statistical analyses

Statistical analysis title	Arm 1 efficacy endpoint statistical analysis
Comparison groups	Arm 1 v Arm 3
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Hochberg and Gatekeeping

Statistical analysis title	Arm 2 efficacy endpoint statistical ana...
Comparison groups	Arm 3 v Arm 2

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Hochberg and Gatekeeping

Secondary: Good European League Against Rheumatism -Responders

End point title	Good European League Against Rheumatism -Responders

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	52	49	
Units: Number of responders				
number (not applicable)	21	26	10	

Statistical analyses

Statistical analysis title	Arm 1 efficacy endpoint statistical analysis
Comparison groups	Arm 1 v Arm 3
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Hochberg and Gatekeeping

Statistical analysis title	Arm 2 efficacy endpoint statistical ana...
Comparison groups	Arm 2 v Arm 3
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Hochberg and Gatekeeping

Secondary: Good/Moderate European League Against Rheumatism Responders	
End point title	Good/Moderate European League Against Rheumatism Responders
End point description:	
End point type	Secondary
End point timeframe: Day 15	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	52	49	
Units: Number of responders				
number (not applicable)	42	43	42	

Statistical analyses

Statistical analysis title	Arm 1 efficacy endpoint statistical analysis
Comparison groups	Arm 1 v Arm 3
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Hochberg and Gatekeeping

Statistical analysis title	Arm 2 efficacy endpoint statistical ana...
Comparison groups	Arm 2 v Arm 3
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.339
Method	Hochberg and Gatekeeping

Secondary: Good European League Against Rheumatism Responders	
End point title	Good European League Against Rheumatism Responders
End point description:	
End point type	Secondary
End point timeframe: Day 15	

End point values	Arm 1	Arm 2	Arm 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	52	49	
Units: Number of responders				
number (not applicable)	24	33	21	

Statistical analyses

Statistical analysis title	Arm 1 efficacy endpoint statistical analysis
Comparison groups	Arm 1 v Arm 3
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.573
Method	Hochberg and Gatekeeping

Statistical analysis title	Arm 2 efficacy endpoint statistical ana...
Comparison groups	Arm 2 v Arm 3
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.374
Method	Hochberg and Gatekeeping

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Week 12	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19
Reporting groups	
Reporting group title	Treatment I
Reporting group description: -	
Reporting group title	Treatment II
Reporting group description: -	
Reporting group title	Treatment III
Reporting group description: -	

Serious adverse events	Treatment I	Treatment II	Treatment III
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 49 (8.16%)	1 / 52 (1.92%)	2 / 49 (4.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 49 (0.00%)	0 / 52 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	0 / 49 (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
Immune system disorders			
Hypersensitivity	Additional description: In Treatment I group, the event of hypersensitivity was unlikely related to IM injection and probably related to IV infusion. In Treatment II group, the event of hypersensitivity was not related to IM injection and related to IV infusion.		

subjects affected / exposed	1 / 49 (2.04%)	1 / 52 (1.92%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	0 / 49 (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
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 52 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 49 (2.04%)	0 / 52 (0.00%)	0 / 49 (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

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

Non-serious adverse events	Treatment I	Treatment II	Treatment III
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 49 (85.71%)	46 / 52 (88.46%)	39 / 49 (79.59%)
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 49 (8.16%)	6 / 52 (11.54%)	6 / 49 (12.24%)
occurrences (all)	4	6	6
Nervous system disorders			
Dizziness	Additional description: One of the subjects in Treatment group I had Dizziness Exertional.		
subjects affected / exposed	4 / 49 (8.16%)	2 / 52 (3.85%)	2 / 49 (4.08%)
occurrences (all)	5	2	2
Headache	Additional description: One of the subjects in Treatment group III had Tension Headache.		
subjects affected / exposed	8 / 49 (16.33%)	9 / 52 (17.31%)	6 / 49 (12.24%)
occurrences (all)	11	9	9

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 49 (12.24%)	6 / 52 (11.54%)	5 / 49 (10.20%)
occurrences (all)	6	7	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 49 (18.37%)	6 / 52 (11.54%)	1 / 49 (2.04%)
occurrences (all)	9	7	1
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: One of the 3 subjects in the Treatment group II had Production Cough.		
subjects affected / exposed	4 / 49 (8.16%)	2 / 52 (3.85%)	4 / 49 (8.16%)
occurrences (all)	4	3	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 49 (12.24%)	5 / 52 (9.62%)	4 / 49 (8.16%)
occurrences (all)	6	6	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2016	The Rheumatoid Arthritis diagnosis selection criterion was amended in Amendment 2. There were no other major changes in the amended protocols.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported