Clinical trial results:
Efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure

Summary

EudraCT number	2008-007407-86
Trial protocol	AT GR DE
Global end of trial date	31 January 2013

Results information

Result version number	v1 (current)
This version publication date	05 June 2020
First version publication date	05 June 2020
Summary attachment (see zip file)	Study Protocol Summary (Study Protocol Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	LevoRep

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01065194
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020
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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	01 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of the study was to compare the effects of a pulsed application of levosimendan versus placebo of the composite end-point functional capacity and quality of life.

Protection of trial subjects:

In clinical studies of levosimendan the drug has been well tolerated. It appears, that levosimendan can be safely combined with drugs commonly prescribed for the treatment of heart failure.
Medical surveillance was continued for additional three hours after completion of study drug administration before patients' discharge. If severe hypotension occured during levosimendan infusion despite optimized fluid management dose of study medication was cut in halve. In case of persisting hypotension study medication has been stopped temporarily and reinstalled if considered appropriate by the treating physician.

Background therapy:

Patients should have been on optimized background therapy according to the ESC-guidelines for the treatment of chronic heart failure, including RAAS-antagonist and Beta-Blocker. Changes or improvement in heart failure medication - if needed - were allowed throughout the study period except for the additional administration of levosimendan. Patients, who received levosimendan out of the protocol during the study period, have been managed as dropouts at the time of drug delivery.

Evidence for comparator:

Based on previously reported data, the prospective, randomized, double-blind, placebo-controlled LevoRep study was designed to test the hypothesis that repeated short-term administration of levosimendan is safe and effective in advanced heart failure patients.

Actual start date of recruitment	27 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 88
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 26
Worldwide total number of subjects	120
EEA total number of subjects	120

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	76
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Patients have been recruited to this study from either the outpatient clinic or inpatient hospital setting at each center. All patients have been seen by the corresponding co-investigator and have been required to sign a written informed consent prior to being registered on this protocol.

Pre-assignment

Screening details:

After a screening period of one week, patients were randomized to levosimendan or placebo in a 1:1 ratio.
Randomization was conducted using computer-generated permutated blocks and stratified according to study center.

Period 1

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

Blinding implementation details:

The placebo infusion was coloured identically to its respective active counterpart. Patients and investigators were kept blinded to treatment allocation for the entire duration of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Levosimendan group

Arm description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients underwent pulsed administration of four cycles of levosimendan at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h at a dose of 0.2 µg/kg/min, without a bolus.

Arm type	Active comparator
Investigational medicinal product name	Levosimendan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Levosimendan 2,5mg/ml infusion concentrate consisted of a 5ml sterile solution in clear rubberstoppered glass vials. It was administered as an intravenous infusion (50 µg /ml in 5% glucose) through a peripheral line according to the predefined treatment plan.

Arm title	Placebo group

Arm description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of placebo at 2-week intervals. Study drug was infused on an ambulatory basis for 6h without a bolus.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo infusion concentrate consisted of a 5ml sterile solution in clear rubberstoppered glass vials. Placebo was infused on an outpatient basis for six hours without a bolus.

Number of subjects in period 1	Levosimendan group	Placebo group
Started	63	57
Completed	53	51
Not completed	10	6
Physician decision	2	1
Consent withdrawn by subject	2	-
additional administration of Levosimendan	-	1
Adverse event, non-fatal	1	-
Death	1	2
Acute heart failure	2	-
HTx	-	1
Protocol deviation	1	-
Noncompliance	1	1

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patients and investigators were kept blinded to treatment allocation for the entire duration of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Levosimendan group

Arm description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of levosimendan at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h at a dose of 0.2 µg/kg/min, without a bolus.

Arm type	Active comparator

Investigational medicinal product name	Levosimendan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Levosimendan 2,5mg/ml infusion concentrate consisted of a 5ml sterile solution in clear rubberstoppered glass vials. It was administered as an intravenous infusion (50 µg /ml in 5% glucose) through a peripheral line according to the predefined treatment plan.

Arm title	Placebo group

Arm description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of placebo at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h without a bolus.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo infusion concentrate consisted of a 5ml sterile solution in clear rubberstoppered glass vials. Placebo was infused on an outpatient basis for six hours without a bolus.

Number of subjects in period 2	Levosimendan group	Placebo group
Started	53	51
Short-term follow-up	53	51
Long-term follow-up	50	43
Completed	50	43
Not completed	3	8
additional administration of Levosimendan	1	3
Adverse event, non-fatal	-	1
Death	-	2
HTx	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Levosimendan group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients underwent pulsed administration of four cycles of levosimendan at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h at a dose of 0.2 µg/kg/min, without a bolus.

Reporting group title	Placebo group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of placebo at 2-week intervals. Study drug was infused on an ambulatory basis for 6h without a bolus.

Reporting group values	Levosimendan group	Placebo group	Total
Number of subjects	63	57	120
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	17	37
From 65-84 years	38	38	76
85 years and over	5	2	7
Age continuous Units: years			
arithmetic mean	69.5	69.5	
standard deviation	± 11.5	± 10.5	-
Gender categorical Units: Subjects			
Female	13	12	25
Male	50	45	95
Gender distribution Units: Subjects			
Female 18-64 years	4	4	8
Male 18-64 years	16	13	29
Female 65-84 years	8	7	15
Male 65-84 years	30	31	61
Female 85 years and over	1	1	2
Male 85 years and over	4	1	5

End points

End points reporting groups

Reporting group title	Levosimendan group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients underwent pulsed administration of four cycles of levosimendan at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h at a dose of 0.2 µg/kg/min, without a bolus.

Reporting group title	Placebo group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of placebo at 2-week intervals. Study drug was infused on an ambulatory basis for 6h without a bolus.

Reporting group title	Levosimendan group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of levosimendan at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h at a dose of 0.2 µg/kg/min, without a bolus.

Reporting group title	Placebo group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of placebo at 2-week intervals. Study drug was infused on an ambulatory basis for 6 h without a bolus.

Primary: Effects of treatment with levosimendan versus placebo in the six minute walk test

End point title	Effects of treatment with levosimendan versus placebo in the six minute walk test

End point description:

The primary efficacy objective of the study was to compare the effects of a pulsed application of levosimendan versus placebo on the composite end-point functional capacity and quality of life. The primary endpoint was defined as the proportion of patients showing an improvement in the six minute walk test of 20% or more at the end of the 24 week study period.

End point type	Primary

End point timeframe:

Day 0- 24 weeks from randomization

End point values	Levosimendan group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	43		
Units: meter				
arithmetic mean (standard deviation)				
Improvements from baseline after 24 weeks	29 (± 80)	34 (± 73)		

Statistical analyses

Statistical analysis title	Effects of treatment with levosimendan and placebo
Comparison groups	Levosimendan group v Placebo group
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.56
Method	Fisher exact

Notes:

[1] - Differences between groups were not significant for improvements in the six min walk test.

Primary: Effects of treatment with levosimendan versus placebo in KCCQ

End point title	Effects of treatment with levosimendan versus placebo in KCCQ

End point description:

The primary efficacy objective of the study was to compare the effects of a pulsed application of levosimendan versus placebo on the composite end-point functional capacity and quality of life. The primary endpoint was defined as the proportion of patients showing a 15% or higher scoring in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at the end of the 24 week study period.

End point type	Primary

End point timeframe:

Day 0- 24 weeks from randomization

End point values	Levosimendan group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	43		
Units: scores				
arithmetic mean (standard deviation)				
Improvements from baseline after 24 weeks	11.5 (± 19)	9.6 (± 16)		

Statistical analyses

Statistical analysis title	Effects of treatment with levosimendan and placebo
Comparison groups	Levosimendan group v Placebo group

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Event-free survival

End point title	Event-free survival

End point description:

The secondary efficacy objective was to determine the effects of a pulsed administration of levosimendan on long-term (24 weeks from randomization) event-free survival (cardiac death or heart failure-related hospitalization).

End point type	Secondary

End point timeframe:

Day 0- 24 weeks from randomization

End point values	Levosimendan group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	43		
Units: events				
number (not applicable)				
No. of event-free patients	11	20		

Statistical analyses

Statistical analysis title	Effects of treatment with levosimendan and placebo
Comparison groups	Levosimendan group v Placebo group
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.98

Adverse events

Adverse events information

Timeframe for reporting adverse events:

03.09.2009-12.11.2012

Adverse event reporting additional description:

Advanced heart failure (AHF) is associated with high morbidity and mortality. Affected patients suffer from severely debilitating symptoms leading to repeat hospital admissions. In total 35 SAEs and 74 AEs have been observed for the levosimendan group and 24 SAEs and 79 AEs for the placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Levosimendan group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of levosimendan at 2-week intervals. Study drug was infused on an ambulatory basis for
6 h at a dose of 0.2 µg/kg/min, without a bolus.

Reporting group title	Placebo group

Reporting group description:

The total study period comprised a 6-week treatment period and an 18-week follow-up period. During the treatment period, patients
underwent pulsed administration of four cycles of placebo at 2-week intervals. Study drug was infused on an ambulatory basis for
6 h without a bolus.

Serious adverse events	Levosimendan group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 63 (36.51%)	19 / 57 (33.33%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Heart transplant			
subjects affected / exposed	1 / 63 (1.59%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 63 (1.59%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ICD Problems			

subjects affected / exposed	2 / 63 (3.17%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	3 / 63 (4.76%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 63 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac decompensation			
subjects affected / exposed	4 / 63 (6.35%)	4 / 57 (7.02%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Synkope			
subjects affected / exposed	1 / 63 (1.59%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	2 / 63 (3.17%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Shortness of breath			
subjects affected / exposed	2 / 63 (3.17%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection			

subjects affected / exposed	1 / 63 (1.59%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dispnoea			
subjects affected / exposed	3 / 63 (4.76%)	3 / 57 (5.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
COPD			
subjects affected / exposed	0 / 63 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	Levosimendan group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 63 (50.79%)	28 / 57 (49.12%)	
Cardiac disorders			
Hypotension			
subjects affected / exposed	20 / 63 (31.75%)	10 / 57 (17.54%)	
occurrences (all)	30	30	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 63 (3.17%)	3 / 57 (5.26%)	
occurrences (all)	5	5	
Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	4	4	
Back pain			
subjects affected / exposed	0 / 63 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Edema			
subjects affected / exposed	3 / 63 (4.76%)	2 / 57 (3.51%)	
occurrences (all)	5	5	

Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	3 / 63 (4.76%)	4 / 57 (7.02%)	
occurrences (all)	7	7	
Nausea			
subjects affected / exposed	0 / 63 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 63 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	5	5	
Shortness of breath			
subjects affected / exposed	4 / 63 (6.35%)	0 / 57 (0.00%)	
occurrences (all)	4	4	
Respiratory infection			
subjects affected / exposed	1 / 63 (1.59%)	2 / 57 (3.51%)	
occurrences (all)	3	3	
COPD			
subjects affected / exposed	0 / 63 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Humid pulmonary rales			
subjects affected / exposed	0 / 63 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	2 / 63 (3.17%)	0 / 57 (0.00%)	
occurrences (all)	2	2	
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 63 (3.17%)	1 / 57 (1.75%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2008	6.2.2 Exclusion criterium: Female patients who are pregnant or nursing 6.2.7 Remuneration: Remuneration will be provided for each study related visit, according to effective costs, not exceeding € 25, - per visit. 6.4.1 Treatment Plan: After randomization patient will enter the treatment period, which will last for six weeks. Levosimendan will be infused on an outpatient basis for six hours at a dosage of 0,2 µg/kg/min without a bolus. Medical surveillance will be continued for additional three hours after completion of study drug administration before patients' discharge. Diuretics should be withheld at the day of study drug administration. If severe hypotension occurs during levosimendan infusion despite optimized fluid anagement dose of study medication will be cut in halve (= 0.1 mg/kg/min). In case of persisting hypotension study medication will be stopped temporarily and reinstalled if considered appropriate by the treating physician. Drug administration will be performed in intervals of two weeks (+/-3days). Following the treatment period patients enter the followup- period, which will last for additional 18 weeks. Follow-up visits will be scheduled at two weeks and 18 weeks, respectively, after finishing the treatment period. 6.5.1 Laboratory Tests: Prior to each administration of Levosimendan and each follow-up visit blood will be taken: 3 Venous serum samples and 2 plasma samples (45mls) will be collected and centrifuged for 10 min at 40°C. 3 aliquots of serum and 2 aliquots of plasma will be stored at – 70°C for testing the following parameters. - Markers of inflammatory activation (IL-6, IL-10 and TNF-alpha) and of the apoptotic process (Afas, SFAS Ligand) - Markers of oxidative stress (MDA, protein carbonyls, nitrotyrosine) - NT-pro-BNP 1 EDTA Blood sample will be drawn for testing Hb, Htk, Thrombocytes, Leucocytes, Na, K, Creatinin; A pregnancy test will be performed before inclusion of the female participant into the trial.
19 February 2009	4.5 Blinding: Will be performed by a certified company or institution (Anstaltsapotheke or Abbott).
20 March 2009	6.5.1 Laboratory Tests: Prior to each administration of Levosimendan and each follow-up visit blood will be taken: 3 Venous serum samples and 2 EDTA plasma samples (45mls) will be collected and centrifuged at 1600 g (RCF – relative centrifugal force) for 10 min at room temperature. 3 aliquots of serum and 2 aliquots of plasma will be stored at – 70°C for testing the following parameters. 6.5.4 Kansas City Cardiomyopathy Questionaire: Questionnaires will be stored in studycenter. 6.4.1. Treatment Plan: Diuretics should be withheld at the day of study drug administration. If severe hypotension occurs during levosimendan infusion despite optimized fluid management dose of study medication will be cut in halve (= 0.1 µg/kg/min). In case of persisting hypotension study medication will be stopped temporarily and reinstalled if considered appropriate by the treating physician. Drug administration will be performed in intervals of two weeks (+/-3days). In total study drug will be administered 4 times throughout the study period, requiring 4 vials of the allocated medication.
21 December 2009	6.2.2. Exclusion Criterium: Implantation of a cardiac resynchronisation device during the last three months 5.2 Secondary efficacy objectives: Cardiac death will be divided into arrhythmic death and pump failure death. Adjudication of endpoints is assigned to the independent Data Safety and Monitoring Board.

15 July 2010	4.1. Levosimendan: Levosimendan (Simdax) is manufactured by Orion Pharma, Espoo, Finland and will be supplied by PharMore. 6.1.2. Timing of the study: The study will start in September 2009. Randomization of the patients will be finished at the end of 2011. Final results should be available in the second quarter of 2012. 7.3. Reporting Procedures: According to the current local law in the event of an SAE and unexpected adverse events report must be made to the ethics committee, AGES and Orion Pharma Finland. The Pharmakovigilance Center, who is informed by the Investigator within 24 hours reports the SAE`s respectively SUSARs to Orion Pharma Finland.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20083626

http://www.ncbi.nlm.nih.gov/pubmed/24920349

http://www.ncbi.nlm.nih.gov/pubmed/28571618

http://www.ncbi.nlm.nih.gov/pubmed/30555280