Clinical trial results:
Safety, PK/PD and efficacy of lexaptepid pegol in dialysis patients with ESA-hyporesponsive anaemia: A randomized, double blind, placebo controlled parallel group study with a single blind cross-over group

Summary

EudraCT number	2013-003585-14
Trial protocol	GB DE AT IT
Global end of trial date	16 November 2015

Results information

Result version number	v1 (current)
This version publication date	25 November 2016
First version publication date	25 November 2016

Trial information

Trial identification

Sponsor protocol code	SNOXH94C301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	NOXXON Pharma AG
Sponsor organisation address	Max-Dohrn-Strasse 8-10, Berlin, Germany, 10589
Public contact	Clinical Trial Disclosure Desk NOXXON, NOXXON Pharma AG, clinicaltrialdisclosuredesk@noxxon.com
Scientific contact	Clinical Trial Disclosure Desk NOXXON, NOXXON Pharma AG, clinicaltrialdisclosuredesk@noxxon.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	15 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2015
Global end of trial reached?	Yes
Global end of trial date	16 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of single and repeated doses of lexaptepid pegol in dialysis patients

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, 2005/28/EC, and 2003/63/EC and relevant national and local legislations, and with the ethical principles that have their origin in the Declaration of Helsinki. Only subjects that met all the study inclusion and none of the exclusion criteria were randomized. Study drug administrations were performed by qualified and trained study personnel. Patients who received treatment were closely followed by means of adverse event reporting and vital signs. In the event of a study related adverse event, patient were monitored to determine the outcome. The clinical course of the AE was followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Investigator considers it medically justifiable to terminate follow-up.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	13
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 12 (Part I) and 42 (Part II) patients were screened and thereof 3 patients in Part I and 16 in Part II were screen failures and 2 dropped out from Part II before any treatment.
Patients started treatment after a screening period of maximum 28 days.

Period 1

Period 1 title	Part 1 and Part 2 - overall 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:

Part 1 was a single dose cross-over, placebo-controlled, single blinded (patient) study;
Part 2 was a repeated dose, 1:1 randomized, placebo-controlled, double blind, parallel-group study

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Crossover

Arm description:

Single dose Placebo (Day 1) followed by single dose lexaptepid pegol (Day 8)

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients received on Day 1 a single dose of placebo by slow injection over 1 minute.
Formulation was a preservative-free, sterile solution in an aqueous citrate buffer containing sucrose.

Investigational medicinal product name	Lexaptepid pegol
Investigational medicinal product code	NOX-H94
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients received on Day 8 a single dose of 1.2 mg/kg lexaptepid pegol administered by slow injection over 1 minute.
Formulation was a preservative-free, sterile solution in an aqueous citrate buffer containing sucrose.

Arm title	Part 2 - Placebo

Arm description:

Repeated dose, randomized, placebo-controlled, double blind, parallel-group

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

twice weekly doses. Nine doses were administered over a treatment period of 4 weeks.
Formulation was a preservative-free, sterile solution in an aqueous citrate buffer containing sucrose.

Arm title	Part 2 - Lexaptepid pegol

Arm description:

Repeated dose, randomized, placebo-controlled, double blind, parallel-group

Arm type	Experimental
Investigational medicinal product name	Lexaptepid pegol
Investigational medicinal product code	NOX-H94
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

twice weekly doses. Nine doses were administered over a treatment period of 4 weeks.
Formulation was a preservative-free, sterile solution in an aqueous citrate buffer containing sucrose.

Number of subjects in period 1	Part 1 - Crossover	Part 2 - Placebo	Part 2 - Lexaptepid pegol
Started	9	12	12
Completed	8	12	11
Not completed	1	0	1
death	-	-	1
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 - Crossover
Reporting group description:	
Single dose Placebo (Day 1) followed by single dose lexaptepid pegol (Day 8)	
Reporting group title	Part 2 - Placebo
Reporting group description:	
Repeated dose, randomized, placebo-controlled, double blind, parallel-group	
Reporting group title	Part 2 - Lexaptepid pegol
Reporting group description:	
Repeated dose, randomized, placebo-controlled, double blind, parallel-group	

Reporting group values	Part 1 - Crossover	Part 2 - Placebo	Part 2 - Lexaptepid pegol
Number of subjects	9	12	12
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean full range (min-max)	 57.6 41 to 73	 70.8 52 to 82	 68.3 50 to 81
Gender categorical Units: Subjects			
Female	6	4	6
Male	3	8	6

Reporting group values	Total		
Number of subjects	33		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	16		
Male	17		

End points

End points reporting groups

Reporting group title	Part 1 - Crossover
Reporting group description:	
Single dose Placebo (Day 1) followed by single dose lexaptepid pegol (Day 8)	
Reporting group title	Part 2 - Placebo
Reporting group description:	
Repeated dose, randomized, placebo-controlled, double blind, parallel-group	
Reporting group title	Part 2 - Lexaptepid pegol
Reporting group description:	
Repeated dose, randomized, placebo-controlled, double blind, parallel-group	

Primary: Safety

End point title	Safety[1]

End point description:

End point type	Primary

End point timeframe:

at any time from treatment start until end of follow-up

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Adverse events were analyzed on patient basis and on event basis, i.e. the number of events and the number and percentage of patients with at least one (specific) event were displayed for each adverse event type.

End point values	Part 1 - Crossover	Part 2 - Placebo	Part 2 - Lexaptepid pegol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	12	12	
Units: Number of patients with TEAEs				
Patients with treatment emergent adverse events	6	10	7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: any time from treatment start until end of follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Part 1 - Crossover
Reporting group description: Single dose Placebo (Day 1) followed by single dose lexaptepid pegol (Day 8)	
Reporting group title	Part 2 - Placebo
Reporting group description: Repeated dose, randomized, placebo-controlled, double blind, parallel-group	
Reporting group title	Part 2 - Lexaptepid pegol
Reporting group description: Repeated dose, randomized, placebo-controlled, double blind, parallel-group	

Serious adverse events	Part 1 - Crossover	Part 2 - Placebo	Part 2 - Lexaptepid pegol
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	2 / 12 (16.67%)	3 / 12 (25.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (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
Peripheral artery stenosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (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

Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (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			
Infusion site cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Part 1 - Crossover	Part 2 - Placebo	Part 2 - Lexaptepid pegol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 9 (66.67%)	10 / 12 (83.33%)	7 / 12 (58.33%)
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypertension			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Peripheral artery stenosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Local swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Skin injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Small intestinal obstruction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1

Infusion site cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Osteomyelitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Hyperphosphataemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2014	Version 3.0: Addition of sTfR and IL-6 as additional pharmacodynamic parameters for secondary endpoint analyses (UK)
20 August 2014	Version 4.1: Change of inclusion criterion 6. The threshold for ferritin was changed from ≥ 500 ng/mL to ≥ 300 ng/mL. Stratification by CHr value (≤ 25 pg or > 25 pg) described. (UK)
28 October 2014	Version 6.0: The total number of patients to enter the study was raised to 32, leading to a 1:1 ratio for lexaptepid pegol and placebo with 12 planned patients in each group in Part II. The study was extended from sites in the United Kingdom to sites in Germany. Optional analyses and sub-studies were specified. These are not part of the present report. (UK, DE)
15 May 2015	Version 7.0: A maximum dose of 120 mg lexaptepid pegol was defined for patients weighing more than 100 kg. The study was extended from sites in the United Kingdom and in Germany to sites in Austria and Italy. (UK, DE, AT, IT)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported