Clinical trial results:
A phase IIa study to characterize the effects of CCL2 inhibition with the Spiegelmer® NOX-E36 in patients with type 2 diabetes mellitus and albuminuria.

Summary

EudraCT number	2011-005710-11
Trial protocol	DE HU PL CZ
Global end of trial date	03 December 2013

Results information

Result version number	v1 (current)
This version publication date	03 February 2016
First version publication date	28 June 2015

Trial information

Trial identification

Sponsor protocol code	SNOXE36C301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01547897
WHO universal trial number (UTN)	-
Other trial identifiers	study number: SNOXE36C301

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	26 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2013
Global end of trial reached?	Yes
Global end of trial date	03 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the effects of 12 weeks treatment with study drug on albumin-creatinine ratio (ACR) in patients with type 2 diabetes and albuminuria

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. Patient 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 would have been monitored to determine the outcome. The clinical course of the AE will be 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:

Stable (unchanged medication for at least 3 months) treatment to control hypertension, hyperglycemia and (if applicable) dyslipidemia;

Stable treatment with angiotensin-converting enzyme inhibitors (ACEi) and/or Angiotensin II receptor blockers (ARBs) (renin-angiotensin system [RAS] blockade

Evidence for comparator: -

Actual start date of recruitment	28 March 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	Czech Republic: 18
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Romania: 1
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	53
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

215 patients were screened, 139 screen failed, after a screening period of up to 30 days duration, to ensure that the patient is stable on his/her concomitant therapy and life style 76 were randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Empapticap

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Empapticap Pegol
Investigational medicinal product code	NOX-E36
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mg/kg body weight two times per week over the 12 weeks treatment period;
a single-use, preservative-free, sterile solution of empapticap in an aqueous phosphate buffer pH 7 with EDTA and glucose for adjustment of tonicity to physiological levels

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

0.5 mg/kg body weight two times per week over the 12 weeks treatment period;
a single-use, preservative-free, sterile solution of glucose, controlled to have physiological pH

Number of subjects in period 1	Empaticap	Placebo
Started	51	25
Completed	46	25
Not completed	5	0
Adverse event, non-fatal	3	-
failure to comply with study stipulations	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Empaticap
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Empaticap	Placebo	Total
Number of subjects	51	25	76
Age categorical Units: Subjects			
Adults (18-64 years)	36	17	53
From 65-84 years	15	8	23
Age continuous Units: years			
arithmetic mean	61.9	61	
full range (min-max)	50 to 83	45 to 76	-
Gender categorical Units: Subjects			
Female	11	7	18
Male	40	18	58

End points

End points reporting groups

Reporting group title	Empacticap
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change from baseline in ACR at the end of 12 weeks treatment

End point title	Change from baseline in ACR at the end of 12 weeks treatment

End point description:

The primary efficacy parameter is the effect of study drug on the change in ACR (Day 85 minus baseline) and was compared to placebo by ANCOVA using the additional factor gender and the covariates age, baseline ACR, and baseline hsCRP.
ANCOVA was performed based on the log-transformed data. The results were back-transformed to the original scale.

End point type	Primary

End point timeframe:

Baseline and Day 85

End point values	Empacticap	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	25		
Units: mg/g				
least squares mean (confidence interval 95%)	0.71 (0.6 to 0.841)	0.84 (0.664 to 1.063)		

Statistical analyses

Statistical analysis title	Empacticap vs Placebo
Comparison groups	Empacticap v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221
Method	ANCOVA
Parameter estimate	geometric least square means ratio
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.645
upper limit	1.108

Secondary: Change from baseline in HbA1c at the end of 12 weeks treatment

End point title	Change from baseline in HbA1c at the end of 12 weeks treatment

End point description:

Change in HbA1c (Day 85 minus baseline) compared to placebo by ANCOVA using the additional factor gender and the covariates age and baseline HbA1c.
ANCOVA was performed based on the log-transformed data. The results were back-transformed to the original scale.

End point type	Secondary

End point timeframe:

Baseline and Day 85

End point values	Empaticap	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	25		
Units: percent				
least squares mean (confidence interval 95%)	0.96 (0.93 to 0.992)	0.996 (0.955 to 1.038)		

Statistical analyses

Statistical analysis title	Empaticap vs Placebo
Comparison groups	Empaticap v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	ANCOVA
Parameter estimate	geometric least square means ratio
Point estimate	0.964
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.918
upper limit	1.013

Adverse events

Adverse events information	
Timeframe for reporting adverse events: baseline (Day 1) until end of follow up (Day 169)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Empaticap
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Empaticap	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			

subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic foot			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (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: 2.5 %

Non-serious adverse events	Empaticap	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 51 (50.98%)	9 / 25 (36.00%)	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 51 (1.96%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			

subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Injection site hematoma			
subjects affected / exposed	3 / 51 (5.88%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Injection site pain			
subjects affected / exposed	3 / 51 (5.88%)	0 / 25 (0.00%)	
occurrences (all)	9	0	
Injection site erythema			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 51 (7.84%)	3 / 25 (12.00%)	
occurrences (all)	5	3	
Bronchitis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Erysipelas			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Diabetic foot			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2012	Amendment 1: "Glycemic disorders" was added to the secondary objective: "To evaluate the effect of study drug on markers of glycemic disorders, systemic inflammation, renal and liver disease, and cardiovascular function"; Inclusion criterion 4 was more specified by adding "first": 4) ACR > 100 mg/g calculated 3 times in first morning void urine; The recommendations from EMA dated 22Dec2011 regarding the treatment of diabetic patients with aliskiren in combination with ACE inhibitors or ARBs are taken into account and inclusion criterion 7 was changed to "Stable treatment with angiotensin-converting enzyme inhibitors (ACEi) and/or Angiotensin II receptor blockers (ARBs) (renin-angiotensin system [RAS] blockade)" and exclusion criterion 11 to "Use of thiazolidinedione class drugs, immune suppressants, steroid therapy (except for topical use or inhalation), chronic use of non-steroidal anti-inflammatory drug (NSAIDs), cyclooxygenase type 2 inhibitors (COX-2), two or more diuretic drugs and/or aliskiren"; To reduce the burden for the patients, the oral glucose tolerance test (oGTT) was exchanged by the Homeostasis Model of Insulin Resistance (HOMA–IR, additional measurement of fasting glucose and fasting insulin).
25 September 2012	Amendment 2: The responsible Medical Monitor had changed; Exclusion criterion 13, it was specified that with previous participation in the study randomization was meant; A wrong transcription in formula for the eGFR was corrected; eGFR was included in the interim analysis.
21 December 2012	Amendment 3: Clarification regarding the order of assessments during the screening period; Inclusion criterion 3 was changed to "HbA1c between 6.0% and 10.5%, inclusive" to take recommendation of ADA (Jan 2012) into account; Inclusion criterion 5 "high-sensitivity C-reactive protein (hsCRP) ≥ 3 mg/L" was omitted because of the weak relationship between systemic (serum hsCRP) and local (kidney) inflammation. hsCRP remained as secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported