Clinical trial results:
A multi-centre, open label, uncontrolled, Phase IIa clinical trial evaluating the safety and efficacy of NOX-A12 in combination with a background therapy of bendamustine and rituximab (BR) in previously treated patients with chronic lymphocytic leukemia (CLL)

Summary

EudraCT number	2011-004672-11
Trial protocol	DE BE IT AT
Global end of trial date	24 April 2017

Results information

Result version number	v1 (current)
This version publication date	24 December 2017
First version publication date	24 December 2017

Trial information

Trial identification

Sponsor protocol code	14SNOXA12C201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01486797
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	12 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2017
Global end of trial reached?	Yes
Global end of trial date	24 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of NOX-A12 alone (pilot group only) and in combination with BR.
To determine the complete remission (CR) rate.

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, patients 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 considered it medically justifiable to terminate follow-up.

Background therapy:

bendamustine and rituximab

Evidence for comparator: -

Actual start date of recruitment	21 May 2012
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	Austria: 13
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Italy: 14
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	8
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

32 patients with diagnosis of relapsed/refractory CLL for which bendamustine / rituximab would be given as standard of care were screened; 4 patients were screening failure. After a screening period of 2 weeks 28 patients were enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Olaptesed pegol + BR

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Olaptesed pegol
Investigational medicinal product code	NOX-A12
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pilot group: 1, 2, or 4 mg/kg body weight olaptesed pegol given as single i.v. injections on Day -14. If no DLT occurred, doses given on Day 1 of each 28-day cycle were 1 mg/kg for Cycle 1, 2 mg/kg for Cycle 2 and 4 mg/kg for Cycle 3 and the highest individually titrated doses through cycles 4 to 6.
Expansion group: i.v. injections of 1 mg/kg body weight olaptesed pegol for Cycle 1, 2 mg/kg for Cycle 2 and 4 mg/kg for Cycle 3 given on Day 1 of each 28-day cycle and the highest individually titrated doses through cycles 4 - 6.
Doses were calculated according to screening body weight. In case body weight changed by more than 10%, the dose was re-calculated.
Single-use, preservative-free, sterile solution of olaptesed pegol in an aqueous glucose solution for adjustment of tonicity to physiological levels.

Number of subjects in period 1	Olaptesed pegol + BR
Started	28
Completed	20
Not completed	8
Start of new therapy due to PD	1
Consent withdrawn by subject	3
Adverse event, non-fatal	3
Infective episodes	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	28	28	
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)	8	8	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.3		
full range (min-max)	41 to 79	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	16	16	

End points

End points reporting groups

Reporting group title	Olaptesed pegol + BR

Reporting group description: -

Primary: Complete remission rate

End point title	Complete remission rate[1]

End point description:

The primary efficacy variable was to determine the complete remission rate according to IWCLL guidelines.

End point type	Primary

End point timeframe:

Six (6) 28-day cycles of treatment

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: It was planned to test for a higher CR than the historical control of 15%, based on published CLL data after treatment with BR alone ranging from 9% (Fischer 2011) to 19% (Waldthaler 2011). Recent data with novel drugs inducing lymphocytosis by mechanisms that interfere with the CXCL12/CXCR4 axis (e.g. ibrutinib, idelalisib) cast doubt whether this is a valid assumption. Results suggest that ORR is a more appropriate end-point regarding the MoA of olaptesed. ORR at the end of treatment was 86%.

End point values	Olaptesed pegol + BR			
Subject group type	Reporting group			
Number of subjects analysed	27[2]			
Units: % patients				
Complete remission rate	11			

Notes:

[2] - One patient was without disease assessment and thus excluded from analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time the patient gives informed consent until 30 days after the last NOX-A12 administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Olaptesed pegol + BR

Reporting group description: -

Serious adverse events	Olaptesed pegol + BR		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 28 (53.57%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Parkinson's disease			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			

subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia chlamydial				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Progressive multifocal leukoencephalopathy				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Sepsis				

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Sinusitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Olaptesed pegol + BR		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		

Chest pain subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Chills subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4		
Fatigue subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 5		
General physical health deterioration subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Mucosal inflammation subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Pyrexia subjects affected / exposed occurrences (all)	10 / 28 (35.71%) 13		
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 7		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 6		
Pleural effusion subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		

Investigations Weight decreased subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2		
Cardiac disorders Extrasystoles subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 6 / 28 (21.43%) 9 3 / 28 (10.71%) 3 3 / 28 (10.71%) 3 17 / 28 (60.71%) 37 5 / 28 (17.86%) 7		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	 3 / 28 (10.71%) 3 7 / 28 (25.00%) 9		

subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	11 / 28 (39.29%)		
occurrences (all)	17		
Stomatitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Hyperhidrosis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Metabolism and nutrition disorders			

Hypokalaemia subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 6		
Hyperuricaemia subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 6		
Decreased appetite subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Dehydration subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Iron deficiency subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Tumour lysis syndrome subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2012	IC8: permissible forms of reliable contraceptive methods are included in the IC, as per 'Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals' (CPMP/ICJ/286/95, amendment) EC5: initial EC5 appears to be in conflict with IC5: "Subject must have measurable disease according to IWCLL criteria (Hallek et al.)." With respect to the WBC, the guideline states: Progr. lymphocytosis with an increase of more than 50% over a 2-mth period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by lin. reg. extrapolation of abs. lymphocyte counts obtained at intervals of 2 wks over an observation period of 2-3 mths. In pts with initial blood lymphocyte counts of <30,000/µL, LDT should not be used as a single parameter to define a treatment indication. Pts with CLL may present with a markedly elevated leukocyte count; however, the symptoms associated with leukocyte aggregates that develop in pts with acute leukemia rarely occur in pts with CLL. Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment. In CLL pts, symptoms of leukostasis are rare unless the WBC count exceeds 400,000/µL. This is mainly due to the fact that malignant B cells are much smaller than, for example, malignant cells of the myeloid lineage seen in AML and CML EC15: add. safety measure, pts with concomitant diseases; e.g. heart diseases; will be excluded from the study Add. safety measure: pts with contraindications noted in the rituximab and bendamustine SPCs will be excluded from the study Add. PK/SDF-1 samples to allow assessment of plasma clearance and half-life of NOX-A12 in combination with BR Clarification: ECGs, vitals, samples for PK/SDF-1 & CD34+ & CLL cell analysis are taken 1 h after NOX-A12, and before BR Add. safety measure and clarification: investigators will assess event relationship to NOX-A12, rituximab and bendamustine and will be included in listings and tables
10 July 2012	In accordance with ANSM request, contraception prolonged to duration specified in SmPC for background therapies. In accordance with ANSM request, additional pregnancy tests each cycle to ensure continued maintenance of contraception during treatment. In accordance with ANSM request, contraception prolonged to duration specified in SmPC for background therapies. In compliance with bendamustine SmPC, discussion with men of reproductive age regarding infertility risk. In accordance with ANSM request, additional pregnancy tests each cycle to ensure continued maintenance of contraception during treatment.
19 September 2012	Additional samples required in Cycle 4 to show the profile of CD34+ cells and CLL cell counts following repeat dosing of NOX-A12 in combination with chemotherapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported