Clinical trial results:
A Two-Part, Open-Label Phase 1/2 Study to Evaluate Pharmacodynamic Effects and Safety of Olaptesed Pegol Monotherapy and Safety and Efficacy of Olaptesed Pegol / Pembrolizumab Combination Therapy in Metastatic Colorectal and Pancreatic Cancer

Summary

EudraCT number	2016-003657-15
Trial protocol	DE
Global end of trial date	25 March 2020

Results information

Result version number	v1 (current)
This version publication date	08 April 2021
First version publication date	08 April 2021

Trial information

Trial identification

Sponsor protocol code	SNOXA12C601

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03168139
WHO universal trial number (UTN)	-
Other trial identifiers	Keynote: 559

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, +49 30726247100, clinicaltrialdisclosuredesk@noxxon.com
Scientific contact	Clinical Trial Disclosure Desk NOXXON, NOXXON Pharma AG, +49 30726247100, 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	02 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2020
Global end of trial reached?	Yes
Global end of trial date	25 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Monotherapy part:
Pharmacodynamics – evaluation of immune infiltrate changes within the tumor microenvironment induced by CXCL12 inhibition with olaptesed pegol by comparing pre- and post-treatment biopsy specimens

Combination therapy part:
To assess safety and tolerability of olaptesed pegol in combination with pembrolizumab

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: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2017
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	Germany: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	9
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

24 patients with diagnosis metastatic colorectal or metastatic pancreatic cancer were screened; 4 patients were screening failure. After a screening period of 4 weeks 20 patients were enrolled.

Pre-assignment

Screening details:

24 patients with diagnosis metastatic colorectal or metastatic pancreatic cancer were screened; 4 patients were screening failure. After a screening period of 4 weeks 20 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 + pembrolizumab

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:

Monotherapy (MT): Weekly on MT D1 and MT D4 for up to 2 weeks: administration of 300 mg olaptesed pegol

Combination therapy (CT): Treatment with olaptesed pegol in combination with pembrolizumab until progressive disease or limiting toxicity, for a maximum of 24 months in total CT D1 and every three weeks (Q3W) thereafter: 300 mg olaptesed pegol + 200 mg pembrolizumab

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475, Keytruda
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Monotherapy (MT): Weekly on MT D1 and MT D4 for up to 2 weeks: administration of 300 mg olaptesed pegol

Combination therapy (CT): Treatment with olaptesed pegol in combination with pembrolizumab until progressive diseaseor limiting toxicity, for a maximum of 24 months in total CT D1 and every three weeks (Q3W) thereafter: 300 mg olaptesed pegol + 200 mg pembrolizumab

Number of subjects in period 1	Olaptesed pegol + pembrolizumab
Started	20
Completed	16
Not completed	4
Consent withdrawn by subject	1
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
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)	9	9	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65		
full range (min-max)	48 to 82	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	15	15	
Genetic hypermutability status Units: Subjects			
microsatellite instable (MSI)	0	0	
microsatellite stable (MSS)	20	20	
Prior treatment lines including surgery Units: number			
arithmetic mean	5.5		
full range (min-max)	1 to 13	-	
Prior treatment lines excluding surgery Units: number			
arithmetic mean	4.1		
full range (min-max)	1 to 9	-	

End points

End points reporting groups

Reporting group title	Olaptesed pegol + pembrolizumab

Reporting group description: -

Primary: Safety Adverse Events

End point title	Safety Adverse Events[1]

End point description:

End point type	Primary

End point timeframe:

AEs and SAEs were collected from the time the patient gave informed consent until 30 days after the last olaptesed pegol and pembrolizumab dose for non-serious AEs and until 90 days for SAEs

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: No statistical analysis was planned for this endpoint.

End point values	Olaptesed pegol + pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: patients				
Any adverse event	19			
Adverse events related to study treatments	6			
Any serious adverse event	9			
Serious adverse events related to study medication	1			
Grade 3 adverse events	11			
Grade 4 adverse events	0			
Grade 5 adverse events	1			
AEs leading to dose reduction or interruption	2			
AEs leading to discontinuation/withdrawal from stu	0			
Events of Clinical Interest	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety Dose Limiting Toxicities

End point title	Safety Dose Limiting Toxicities[2]

End point description:

DLTs were defined as
- Grade 4 non-hematologic AEs (not laboratory)

- Grade 4 hematologic AE lasting >7d, except thrombocytopenia <25,000/mm³ if associated with bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or life-threatening bleeding event which results in urgent intervention and admission to an ICU
- Grade 3 non-hematologic AE (not laboratory) lasting >3d
- Grade 3 nausea, vomiting or diarrhea if lasting >3d
- Grade 3 or Grade 4 non-hematologic laboratory AE, if medical intervention is required, or to hospitalization, or persists for > 1 week
- Grade 3 or Grade 4 febrile neutropenia
- Grade 5 AE
- AE which caused treatment discontinuation during Cycle 1
- Any AE which delayed initiation of Cycle 2 by >2 weeks

End point type	Primary

End point timeframe:

The period of evaluating DLT was throughout the monotherapy and one 21-day cycle of the combination therapy.

Notes:

[2] - 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: No statistical analysis was planned for this endpoint

End point values	Olaptesed pegol + pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: patients				
Number of patients with DLTs	1			

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	21.1

Reporting groups

Reporting group title	Olaptesed pegol + pembrolizumab

Reporting group description: -

Serious adverse events	Olaptesed pegol + pembrolizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileal perforation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Olaptesed pegol + pembrolizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	5		
International normalised ratio increased			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
White blood cell count increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	7 / 20 (35.00%) 9 5 / 20 (25.00%) 6 3 / 20 (15.00%) 3 3 / 20 (15.00%) 3 2 / 20 (10.00%) 2 2 / 20 (10.00%) 3		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 4		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3 2 / 20 (10.00%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		

Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 2 / 20 (10.00%) 2		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 2 / 20 (10.00%) 2		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) lung infection subjects affected / exposed occurrences (all)	 4 / 20 (20.00%) 5 2 / 20 (10.00%) 2 2 / 20 (10.00%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Iron deficiency subjects affected / exposed occurrences (all)	 3 / 20 (15.00%) 3 3 / 20 (15.00%) 3 2 / 20 (10.00%) 2 2 / 20 (10.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2017	Amendment 1 prepared to comply with the requirements from BfArM and EC during the initial submission.; Changes to the protocol: Addition of most current treatments in inclusion criteria; Update of several exclusion criteria; Added HIV test at screening; Enlarged benefit / risk assessment; Added definition on completion of study; Complete restructuring of section 'selection of doses'; Reworked amended the following sections 'selection of study population', 'patient withdrawal', 'contraception', 'pharmacodynamics', 'pharmacokinetics', 'pharmacogenetics', 'immunogenicity', 'patient information and consent'; Added Reference Safety Information from the current IB
02 May 2017	Amendment 2 Changes requested by MSD on the approved version 1.1; Update of benefit / risk assessment; Changed MSI / MSS status determination to mandatory for PaC patients
29 August 2017	Amendment 3 Added clarifications to inclusion criterion and to the order of assessment in the flow chart
21 December 2017	Amendment 4 Added clarifications to the flow chart and ECG parameters recorded
21 September 2018	Amendment 5 Added collection of additional data during follow-up and to included information about the occurrence of cancer in the family history in medical history

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported