Clinical trial results:
A Single-dose dose escalation trial in a randomised, single-blind, placebo-controlled group-comparison design to investigate the safety and tolerability of XEN-D0501 in 24 patients with diabetes mellitus type 2

Summary

EudraCT number	2016-003843-12
Trial protocol	DK
Global end of trial date	30 August 2019

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	PP-CT01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	PILA PHARMA
Sponsor organisation address	Västergatan 1, Malmö, Sweden, 211 21
Public contact	Dorte X. Gram, PILA PHARMA, 46 739036969, info@pilapharma.com
Scientific contact	Dorte X. Gram, PILA PHARMA, 46 739036969, info@pilapharma.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 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2019
Global end of trial reached?	Yes
Global end of trial date	30 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of single ascending oral doses of XEN-D0501, (1, 2 and 4 mg) versus placebo in type 2 diabetic patients in treatment with metformin.

Protection of trial subjects:

No specific protection other than informing of the potential risk of the study medication and potential pain associated with blood sampling

Background therapy:

No specific background therapy defined/ criteria

Evidence for comparator:

Not applicable

Actual start date of recruitment	10 January 2017
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	Denmark: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in adult subjects with type 2 diabetes mellitus consenting to participate in the trial.
The subjects were recruited directly at the outpatient clinics at Odense University Hospital, Denmark and via the Medicollect Research panel in Denmark

Pre-assignment

Screening details:

1. The subject had to give his/her signed and dated informed consent before any trial-related activities. Trial-related activities are any procedures that would not have been performed during the normal management of the subject.
2. Diagnosis of type 2 diabetes mellitus
3. HbA1C (glycosylated haemoglobin A1C) of 6.5-10 %
4. Age between 30 and 70

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	1 mg XEN-D0501

Arm description:

Single dose of 1 mg XEN-D0501 po

Arm type	Experimental
Investigational medicinal product name	XEN-D0501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1mg single oral dose

Arm title	2 mg XEN-D0501

Arm description:

Single dose of 2 mg XEN-D0501 po

Arm type	Experimental
Investigational medicinal product name	XEN-D0501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg single oral dose

Arm title	4 mg XEN-D0501

Arm description:

Single dose of 4 mg XEN-D0501 po

Arm type	Experimental
Investigational medicinal product name	XEN-D0501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
4 mg single oral dose

Arm title	8 mg XEN-D0501

Arm description:
Single dose of 8 mg XEN-D0501 po

Arm type	Experimental
Investigational medicinal product name	XEN-D0501 8 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Single dose of 8 mg XEN-D0501 po

Arm title	Placebo

Arm description:
Single dose of placebo po

Arm type	Placebo
Investigational medicinal product name	Reference treatment (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
A single oral dose of placebo

Number of subjects in period 1	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501
Started	6	2	6
Completed	6	2	6

Number of subjects in period 1	8 mg XEN-D0501	Placebo
Started	6	6
Completed	6	6

Baseline characteristics

Reporting groups	
Reporting group title	1 mg XEN-D0501
Reporting group description: Single dose of 1 mg XEN-D0501 po	
Reporting group title	2 mg XEN-D0501
Reporting group description: Single dose of 2 mg XEN-D0501 po	
Reporting group title	4 mg XEN-D0501
Reporting group description: Single dose of 4 mg XEN-D0501 po	
Reporting group title	8 mg XEN-D0501
Reporting group description: Single dose of 8 mg XEN-D0501 po	
Reporting group title	Placebo
Reporting group description: Single dose of placebo po	

Reporting group values	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501
Number of subjects	6	2	6
Age categorical Units: Subjects			

Age continuous			
Age at screening			
Units: years			
arithmetic mean	67.0	60.0	57.5
standard deviation	± 2.3	± 2.8	± 11.2
Gender categorical Units: Subjects			
Female	4	1	2
Male	2	1	4

Reporting group values	8 mg XEN-D0501	Placebo	Total
Number of subjects	6	6	26
Age categorical Units: Subjects			

Age continuous			
Age at screening			
Units: years			
arithmetic mean	63.3	60.5	
standard deviation	± 4.5	± 11.9	-
Gender categorical Units: Subjects			
Female	4	1	12
Male	2	5	14

Subject analysis sets	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients enrolled in the study who completed without any major protocol deviations

Reporting group values	Per protocol analysis set		
Number of subjects	26		
Age categorical Units: Subjects			
Age continuous			
Age at screening			
Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female	12		
Male	14		

End points

End points reporting groups

Reporting group title	1 mg XEN-D0501
Reporting group description: Single dose of 1 mg XEN-D0501 po	
Reporting group title	2 mg XEN-D0501
Reporting group description: Single dose of 2 mg XEN-D0501 po	
Reporting group title	4 mg XEN-D0501
Reporting group description: Single dose of 4 mg XEN-D0501 po	
Reporting group title	8 mg XEN-D0501
Reporting group description: Single dose of 8 mg XEN-D0501 po	
Reporting group title	Placebo
Reporting group description: Single dose of placebo po	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description: All patients enrolled in the study who completed without any major protocol deviations	

Primary: Safety and tolerability

End point title	Safety and tolerability[1]
End point description: Recordings of numbers, types and severity of adverse events	
End point type	Primary
End point timeframe: From the first trial related activity after the subject has signed the informed consent and until the end of trial participation.	

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 were performed for the primary endpoint - safety and tolerability of single ascending doses of XEN-D0501 versus placebo.

Details of the safety profile are provided under Adverse events.

End point values	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501	8 mg XEN-D0501
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	6	6
Units: Events				
Adverse events	6	0	9	12

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	6			

Units: Events				
Adverse events	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events / serious adverse events

End point title	Adverse events / serious adverse events

End point description:

End point type	Secondary

End point timeframe:

From signing of informed consent to end of trial

End point values	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501	8 mg XEN-D0501
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	6	6
Units: Events				
Adverse events	6	0	9	12
Serious adverse events	0	0	0	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Events				
Adverse events	1			
Serious adverse events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Hyperthermia events

End point title	Hyperthermia events

End point description:

End point type	Secondary

End point timeframe:

From signing of informed consent to end of trial participation

End point values	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501	8 mg XEN-D0501
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	6	6
Units: Events				
Hyperglycemia events	0	0	0	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Events				
Hyperglycemia events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemic events

End point title	Hypoglycemic events

End point description:

End point type	Secondary

End point timeframe:

From signing of informed consent to end of trial participation

End point values	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501	8 mg XEN-D0501
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	6	6
Units: Events	0	0	0	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - Cmax

End point title	Pharmacokinetics - Cmax[2]

End point description:

End point type	Secondary

End point timeframe:

8 hours after oral administration

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis were performed for the Secondary endpoint Pharmacokinetics - Cmax

End point values	1 mg XEN-D0501	2 mg XEN-D0501	4 mg XEN-D0501	8 mg XEN-D0501
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	6	6
Units: ng/mL				
arithmetic mean (full range (min-max))				
Cmax	18.2 (7.12 to 30.4)	29.9 (27.6 to 32.1)	75.2 (39.5 to 124.0)	143 (62.7 to 286)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial related activity after the subject has signed the informed consent and until the end of trial participation.

Adverse event reporting additional description:

The Internal Safety Review Committee continously surveilled the electronic database for available safety data. Due to previously reported TRPV1-antagonists sideeffects, a special focus was on hyperthermia or hypo-glycemia, liver and renal functions as well as QTc values. Trial continuation/dose escalation was decided after each cohort.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Single dose 1 mg XEN-D0501 po

Reporting group description:

The first cohort of type 2 diabetic patients being exposed to a single oral tablet of 1 mg XEN-D0501.

This was the first exposure ever of XEN-D0501 to patients with type 2 diabetes.

Reporting group title	Single dose 2 mg XEN-D0501 po

Reporting group description:

Second group of type 2 diabetic patients where the dose of XEN-D0501 was doubled to 2 mg.

The cohort was discontinued after 2 patients since regulatory approval was given to go directly to 4 mg due to low incident of adverse events.

Reporting group title	Single dose 4 mg XEN-D0501 po

Reporting group description:

Third group of type 2 diabetic patients where the dose of XEN-D0501 was doubled to 4 mg.

In non-diabetic subjects, the maximal tolerable dose was previously found to be bi-daily doses of 4 mg dosed for up to 28 days. This dose was expected to be the maximal tolerable dose in type 2 diabetics as well.

Reporting group title	Single dose 8 mg XEN-D0501 po

Reporting group description:

Fourth group of type 2 diabetic patients where the dose of XEN-D0501 was doubled to 8 mg.

This dose level was not expected to be well tolerated by type 2 diabetic patients, since, in non-diabetic subjects the maximal tolerable dose was found to be bi-daily doses of 4 mg dosed for up to 28 days.

Reporting group title	Placebo

Reporting group description:

Group of type 2 diabetic patients that were dosed with placebo tablets for comparison.
Two patients were dosed with placebo with each group of XEN-D0501 exposed patients (2 placebo in each cohort).

Serious adverse events	Single dose 1 mg XEN-D0501 po	Single dose 2 mg XEN-D0501 po	Single dose 4 mg XEN-D0501 po
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events

Serious adverse events	Single dose 8 mg XEN-D0501 po	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Single dose 1 mg XEN-D0501 po	Single dose 2 mg XEN-D0501 po	Single dose 4 mg XEN-D0501 po
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	0 / 2 (0.00%)	4 / 6 (66.67%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Feeling cold			
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Feeling hot			
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	3
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Single dose 8 mg XEN-D0501 po	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	1 / 6 (16.67%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Feeling cold			
subjects affected / exposed	4 / 6 (66.67%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Feeling hot			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Hot flush			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Discomfort			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Flatulence subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2016	Amendment to Protocol Version 2.0 Changes made to protocol version 1.0 due to comments from EC 9/11-2016: • New section added to section 7.5, p. 39, information about biobank. • Information about 'total blood loss volume' – added to section 7.5.1, p. 39: (The calculated blood sampling volume per patient is approximately 40 mL in total).
12 February 2017	Changes made to protocol version 2.0 due to comments from DMA 22/12-2016: • Definitions on Adverse reactions (ARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) are added to section 11.1, p. 46: Changes made to protocol version 2.0 due to comments from DMA 22/12-2016: • Definitions on Adverse reactions (ARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) are added to section 11.1, p. 46: Adverse reaction (AR): All noxious and unintended responses to an investigational medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to an investigational medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility – in essence, the relationship cannot be ruled out. Suspected Unexpected Serious Adverse Reaction (SUSAR):A serious adverse event that has a suspected causal relationship with the investigational medicinal product and which is not consistent with the applicable investigator brochure. • Changes to Chapter 7 Methods and assessments: Changes to section 7.1 p. 28, Visit procedures: Change from: 'Each subject will attend two screening visits (V1 and V2) to determine eligibility for participation in the trial. Subjects fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised to one of the given treatments. Randomized subjects will be scheduled to attend a visit 3 where the trial product is dosed (V3) and a follow up visit (V4).' Change to: 'Each subject will attend two screening visits (V1 and V2) to determine eligibility for participation in the trial. Subjects fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised to one of the given treatments. Randomized subjects will be scheduled to attend a visit 3 where the trial product is dosed (V3) and a follow up visit (V4).' .. etc

23 October 2017	• Changes of Inclusion criteria, section 5.2 p. 22, due to lack of patients fulfilling the inclusion criteria: Deletion of the following inclusion criterion: 3. In treatment with metformin, but no other anti- diabetic drugs • Changes of Exclusion criteria, section 5.3 p. 22-24, due to lack of patients: Deletion of the following exclusion criteria: 2. A subject who has a supine blood pressure at screening (including those on anti-hypertensives), after resting for 5 min, outside the range of 90-140 mmHg systolic or 50-90 mmHg diastolic (excluding white-coat hypertension; therefore, if a repeated measurement on a second screening visit shows values within the range, the subject can be included in the trial). 3. A subject who is in pharmacological treatment of hypertension if the current treatment includes other than an ACE-inhibitor 8. A subject who smokes more than 5 cigarettes, or the equivalent, per day and is unable to refrain from smoking during the in-house periods as determined by the Investigator. 15. A subject who has proliferative retinopathy or maculopathy, and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator. Change of exclusion criterion 5 from: 5. A subject who has participated in any other trials involving investigational products within the 3 months preceding the start of dosing. Change of exclusion criterion 5 to: 5. A subject who has participated in any other trials involving investigational products within the 1 month preceding the start of dosing. • Changes of Visit exclusion criteria, section 5.3.1 p. 24-25, due to lack of patients: Deletion of the following visit exclusion criteria: 1. Strenuous exercise within 48 h prior to screening visit to end of follow up visit, as judged by the Investigator. 5. A subject who has used any new non-prescribed systemic medication or topical medication, ... etc

23 April 2018	• Changes in Section 1.1 Objectives: Changed from: (1, 2 and 4 mg) Changed to: (1, 4 and 8 mg) • Changes in Section 1.5 Trial products: Changed from: • Placebo • XEN-D0501, 1 mg/tablet • XEN-D0501, 2 mg/tablet • XEN-D0501, 4 mg/tablet Changed to: • Placebo • XEN-D0501, 1 mg/tablet • XEN-D0501, 4 mg/tablet • XEN-D0501, 8 mg, 2 x 4mg/tablet Changes in Section 3.3 Objectives: Changed from: (1, 2 and 4 mg) Changed to: (1, 4 and 8 mg) Changes in Section 4.2.1 Treatment of subjects: Change from: 1. XEN-D0501, 1 mg p.o. (n=6) and placebo (n=2) 2. XEN-D0501, 2 mg p.o. (n=6) and placebo (n=2) 3. XEN-D0501, 4 mg p.o. (n=6) and placebo (n=2) Change to: 1. XEN-D0501, 1 mg p.o. (n=6) and placebo (n=2) 2. XEN-D0501, 4 mg p.o. (n=6) and placebo (n=2) 3. XEN-D0501, 8 mg p.o. (n=6) and placebo (n=2) Change from: Each subject will be randomised to a given treatment. Cohorts of 8 patients are run subsequently whereof 2 patients receive placebo and 6 patients receive XEN-D0501 beginning with the 1 mg dose followed by the 2 and 4 mg dose groups. Change to: Each subject will be randomised to a given treatment. Cohorts of 8 patients are run subsequently whereof 2 patients receive placebo and 6 patients receive XEN-D0501 beginning with the 1 mg dose followed by the 4 and 8 mg dose groups. • Changes in Section 8.1 Trial products: Changed from: • Placebo • XEN-D0501, 1 mg/tablet • XEN-D0501, 2 mg/tablet • XEN-D0501, 4 mg/tablet Changed to: • Placebo • XEN-D0501, 1 mg/tablet • XEN-D0501, 4 mg/tablet • XEN-D0501, 8 mg, 2 x 4mg/tablet

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/21676011