



## Clinical trial results:

**A double-blind, randomised, placebo-controlled, crossover study to assess the efficacy of XEN-D0501, a TRPV1 antagonist, in reducing the frequency of cough in patients with chronic obstructive pulmonary disease.**

### Summary

EudraCT number	2013-004041-17
Trial protocol	GB
Global end of trial date	25 February 2015

### Results information

Result version number	v1 (current)
This version publication date	09 July 2016
First version publication date	09 July 2016

### Trial information

#### Trial identification

Sponsor protocol code	XEN-D0501-CL-05
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02233699
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Xention Ltd
Sponsor organisation address	Unit 5, Quesrn House, Hinton Way, Great Shelford, United Kingdom, CB22 5LD
Public contact	Chief Medical Officer, Xention Limited, + 44 1223493900, info@xention.com
Scientific contact	Chief Medical Officer, Xention Limited, + 44 1223493900, info@xention.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	25 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2015
Global end of trial reached?	Yes
Global end of trial date	25 February 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the effectiveness of XEN-D0501 over placebo in reducing objective daytime cough frequency.

Protection of trial subjects:

No specific measures

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

Notes:

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**Subjects enrolled per age group**

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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)	10
From 65 to 84 years	17
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening procedures to determine subject eligibility were performed within 28 days prior to the first dose administration

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	XEN-D0501

Arm description:

subjects received XEN-D0501 for 14 days and then matching placebo for an additional period of 14 days with 2 weeks minimum washout period between the 2 treatments.

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

Dosage and administration details:

4 mg XEN-D0501 taken as oral tablet formulation twice daily for 14 days.

<b>Arm title</b>	Placebo
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Arm description:

Subjects received Placebo for 14 days and then XEN-D0501 for an additional period of 14 days with 2 weeks minimum washout period between the 2 treatments.

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

Dosage and administration details:

4 mg matching placebo taken as oral tablet formulation twice daily for 14 days.

<b>Number of subjects in period 1</b>	XEN-D0501	Placebo
Started	27	27
Completed	27	27

## Baseline characteristics

### Reporting groups

Reporting group title	XEN-D0501
Reporting group description: subjects received XEN-D0501 for 14 days and then matching placebo for an additional period of 14 days with 2 weeks minimum washout period between the 2 treatments.	
Reporting group title	Placebo
Reporting group description: Subjects received Placebo for 14 days and then XEN-D0501 for an additional period of 14 days with 2 weeks minimum washout period between the 2 treatments.	

Reporting group values	XEN-D0501	Placebo	Total
Number of subjects	27	27	27
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	10	10
From 65-84 years	17	17	17
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	10	10	10
Male	17	17	17

## End points

### End points reporting groups

Reporting group title	XEN-D0501
Reporting group description: subjects received XEN-D0501 for 14 days and then matching placebo for an additional period of 14 days with 2 weeks minimum washout period between the 2 treatments.	
Reporting group title	Placebo
Reporting group description: Subjects received Placebo for 14 days and then XEN-D0501 for an additional period of 14 days with 2 weeks minimum washout period between the 2 treatments.	

### Primary: change from baseline in the objective daytime cough frequency

End point title	change from baseline in the objective daytime cough frequency
End point description: change from baseline in the objective daytime cough frequency	
End point type	Primary
End point timeframe: after 14 days treatment with XEN-D0501 or placebo	

End point values	XEN-D0501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: coughs per hour				
geometric mean (standard deviation)	-1.35 ( $\pm$ 6.85)	-3.91 ( $\pm$ 11.74)		

### Statistical analyses

Statistical analysis title	Treatmetn ratio of geometric mean
Comparison groups	XEN-D0501 v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6353
Method	Mixed models analysis

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from signing informed consent form to the last patient last visit.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	XEN-D0501
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	XEN-D0501	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (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: 0.05 %

Non-serious adverse events	XEN-D0501	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)	15 / 25 (60.00%)	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 27 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Contusion			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	

Thermal burn subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Joint injury subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Sunburn subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Hot flush subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Nervous system disorders Thermohypoaesthesia subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 8	1 / 25 (4.00%) 1	
Dysgeusia subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 5	0 / 25 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	2 / 25 (8.00%) 2	
Hypogeusia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4	0 / 25 (0.00%) 0	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 25 (4.00%) 1	
Ageusia			



subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Dysaesthesia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	4 / 27 (14.81%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Feeling cold			
subjects affected / exposed	3 / 27 (11.11%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
chilis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Drug intolerance			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Feeling of body temperature change			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Paraesthesia oral			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Dry mouth			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Glossodynia			

subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Hypoaesthesia oral subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Oral mucosal blistering subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	2 / 25 (8.00%) 2	
Cough subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Choking subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Dysphonia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Productive cough subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Rhinorrhoea			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Sputum increased subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Skin and subcutaneous tissue disorders			
Cold sweat subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Dermatitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Rash generalised subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Stasis dermatitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Psychiatric disorders			
Nervousness subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Back pain subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 25 (4.00%) 1	
Infections and infestations			
Folliculitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	
Herpes zoster subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 25 (0.00%) 0	

Rhinitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2013	<ul style="list-style-type: none"><li>• Revised exclusion criterion 8 to list the excluded medications listed in Section 9.8.3 of the protocol</li><li>• Revised inclusion criterion 5 to remove the condition that no contraception was required if the partner was already pregnant</li><li>• Removed specific vendors for SAE reporting and for safety laboratory testing</li><li>• Updated questions 4 and 15 of the LCQ.</li></ul>
25 February 2014	Addition of a baseline VAS diary assessment to comply with study objectives
16 April 2014	<ul style="list-style-type: none"><li>• To document a change of statistician</li><li>• Revised inclusion criterion 2 and exclusion criteria 1 and 10 to reduce the excessive number of screen failures. Changed inclusion criterion 2 to include patients with a pre-bronchodilator FEV1 of at least 1.0 L at Visit 1. Changed exclusion criterion 1 to exclude patients with a BMI &gt;40 kg/m2 and criterion 10 was revised to allow inclusion of patients with Type 2 diabetes, if the Investigators opinion was that they were well controlled and had no history suggestive of autonomic neuropathy</li><li>• Revised the hourly change in cough frequency secondary endpoint so that the endpoint was assessed at the end of each treatment period. The cough severity and urge to cough secondary endpoints were also amended so that the change from Baseline was assessed over each treatment period</li><li>• Revised the statistical methods section to include repeated measure models for the analysis of the hourly change in cough frequency, cough severity and urge to cough secondary endpoints</li><li>• Amended the wording for the safety study population to safety analysis set for consistency.</li></ul>
22 September 2014	<ul style="list-style-type: none"><li>• Removed the requirement for the capsaicin challenge to be completed by all 22 patients, as a sample size of 15 patients was considered sufficient to interpret the data</li><li>• Revised inclusion criteria numbering from 2 to 3 and clarified that only patients included in the capsaicin challenge cohort were required to have a pre-bronchodilator FEV1 of at least 1.0 L at Visit 1 throughout the protocol</li><li>• Added a new exclusion criterion 20 to exclude COPD patients with respiratory failure that required long-term oxygen therapy and revised subsequent exclusion criteria numbering</li><li>• Revised the planned number of patients to allow approximately 25 patients to be randomised to treatment and enable 22 patients to complete the study of which at least 15 patients were to complete the capsaicin challenge</li><li>• Added a new study population for the capsaicin challenge cohort, the CCAS.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported