Clinical trial results:
Repeat-Dose Pharmacokinetic and Pharmacodynamic Evaluation of Cytisine in Healthy Smokers

Summary

EudraCT number	2017-003257-42
Trial protocol	GB
Global end of trial date	05 October 2018

Results information

Result version number	v1
This version publication date	09 October 2019
First version publication date	09 October 2019

Trial information

Trial identification

Sponsor protocol code	ACH-CYT-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03303911
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Achieve Life Sciences Inc
Sponsor organisation address	520 Pike Street Suite 2250, Seattle, United States, 98101
Public contact	Daniel Cain, Vice President, Clinical Research, Achieve Life Sciences Inc, 1 425.686.1546, dcain@achievelifesciences.com
Scientific contact	Daniel Cain, Vice President, Clinical Research, Achieve Life Sciences Inc, 1 425.686.1546, dcain@achievelifesciences.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	05 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were:
• To evaluate the pharmacokinetic (PK) parameters during repeat dosing of 1.5 mg or 3.0 mg cytisine when administered as
the commercial 25-day schedule.
• To evaluate the pharmacodynamic (PD) effects (e.g., reduction in smoking) with repeat dosing of 1.5 mg or 3.0 mg cytisine
when administered as the commercial 25-day schedule.

Protection of trial subjects:

The informed consent forms used for the study comply with the Declaration of Helsinki and its updates and the International Conference on Harmonization (ICH) Guidelines and have been approved by the Sponsor and the Investigator's IRB/EC/REB. The Investigator explained the nature of the study and the treatment in such a manner that the patient was aware of his/her rights and responsibilities, as well as potential benefits and risks. Patients were informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent was recorded in the patient's medical record or a study/clinic chart. Patients, or their legally authorized representative, gave informed consent in writing prior to the performance of any protocol-specific procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 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	United Kingdom: 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)	24
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening assessments were carried out within 28 days before first administration of cytisine. Eligible subjects were asked to return for the treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cytisine 1.5 mg

Arm description:

Multiple doses of 1.5 mg cytisine administered per 25-day schedule:
• Days 1-3 (6 times daily)
• Days 4-12 (5 times daily)
• Days 13-16 (4 times daily)
• Days 17-20 (3 times daily)
• Days 21-24 (2 times daily)
• Day 25 (Once daily)

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

Dosage and administration details:

1 tablet to be taken with 240 mL water for each dose

Arm title	Cytisine 3.0 mg

Arm description:

Multiple doses of 3.0 mg cytisine administered per 25-day schedule:
• Days 1-3 (6 times daily)
• Days 4-12 (5 times daily)
• Days 13-16 (4 times daily)
• Days 17-20 (3 times daily)
• Days 21-24 (2 times daily)
• Day 25 (Once daily)

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

Dosage and administration details:

2 tablets to be taken with 240 mL water for each dose

Number of subjects in period 1	Cytisine 1.5 mg	Cytisine 3.0 mg
Started	13	13
Completed	13	13

Baseline characteristics

Reporting groups	
Reporting group title	Cytisine 1.5 mg
Reporting group description: Multiple doses of 1.5 mg cytisine administered per 25-day schedule: • Days 1-3 (6 times daily) • Days 4-12 (5 times daily) • Days 13-16 (4 times daily) • Days 17-20 (3 times daily) • Days 21-24 (2 times daily) • Day 25 (Once daily)	
Reporting group title	Cytisine 3.0 mg
Reporting group description: Multiple doses of 3.0 mg cytisine administered per 25-day schedule: • Days 1-3 (6 times daily) • Days 4-12 (5 times daily) • Days 13-16 (4 times daily) • Days 17-20 (3 times daily) • Days 21-24 (2 times daily) • Day 25 (Once daily)	

Reporting group values	Cytisine 1.5 mg	Cytisine 3.0 mg	Total
Number of subjects	13	13	26
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	24
From 65-84 years	1	1	2
Age continuous Units: years			
arithmetic mean	37.0	40.9	
standard deviation	± 12.87	± 12.94	-
Gender categorical Units: Subjects			
Female	4	5	9
Male	9	8	17
Race Units: Subjects			
White	13	12	25
Other, not specified	0	1	1
Expired Carbon Monoxide (CO) at Screening Units: ppm			
arithmetic mean	21.0	20.7	
standard deviation	± 8.02	± 6.76	-
Urine Cotinine at Screening Units: ng/mL			
arithmetic mean	1661.0	1944.2	
standard deviation	± 502.57	± 611.16	-
Number of Cigarettes Smoked in the Past 24 hours on Day -1 Units: cigarettes			
arithmetic mean	16.31	18.08	

standard deviation	± 3.401	± 5.171	-
Tobacco Craving Questionnaire - Short Form (TCQSF) Emotionality Score at Day -1			
The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Emotionality scores may range from 3 to 21, with lower scores indicating weaker emotional signs of tobacco craving.			
Units: score on a scale			
arithmetic mean	10.9	11.7	
standard deviation	± 5.25	± 5.28	-
TCQ-SF Expectancy Score at Day -1			
The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Expectancy scores may range from 3 to 21, with lower scores indicating less positive expectations about smoking.			
Units: score on a scale			
arithmetic mean	11.4	14.0	
standard deviation	± 5.19	± 6.47	-
TCQ-SF Compulsivity Score at Day -1			
The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly agree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Compulsivity scores may range from 3 to 21, with lower scores indicating compulsion to smoke was a lesser component of tobacco craving.			
Units: score on a scale			
arithmetic mean	9.5	9.5	
standard deviation	± 4.61	± 4.33	-
TCQ-SF Purposefulness Score at Day -1			
The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Purposefulness scores may range from 3 to 21, with lower scores indicating stronger ability to not smoke.			
Units: score on a scale			
arithmetic mean	14.9	15.6	
standard deviation	± 3.57	± 5.27	-
TCQ-SF Total Score at Day -1			
The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Total scores may range from 12 to 84, with lower scores indicating lower tobacco craving.			
Units: score on a scale			
arithmetic mean	46.7	50.8	
standard deviation	± 12.96	± 16.89	-
Fagerström Test for Nicotine Dependence Total Score at Day -1			
The Fagerström Nicotine Dependence Questionnaire (FTND) is a measure of nicotine dependence. The FTND total score is defined as the sum of the scores from 6 questions, provided all 6 questions have been completed. The FTND responses are assigned numerical values. Total Scores may range from 0 to 10, with lower scores indicating less dependence on nicotine.			
Units: score on a scale			

arithmetic mean	4.7	5.3	
standard deviation	± 1.60	± 1.38	-

End points

End points reporting groups

Reporting group title	Cytisine 1.5 mg

Reporting group description:

Multiple doses of 1.5 mg cytisine administered per 25-day schedule:
• Days 1-3 (6 times daily)
• Days 4-12 (5 times daily)
• Days 13-16 (4 times daily)
• Days 17-20 (3 times daily)
• Days 21-24 (2 times daily)
• Day 25 (Once daily)

Reporting group title	Cytisine 3.0 mg

Reporting group description:

Multiple doses of 3.0 mg cytisine administered per 25-day schedule:
• Days 1-3 (6 times daily)
• Days 4-12 (5 times daily)
• Days 13-16 (4 times daily)
• Days 17-20 (3 times daily)
• Days 21-24 (2 times daily)
• Day 25 (Once daily)

Subject analysis set title	Pharmacokinetic Set: Cytisine 1.5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who completed all cytisine 1.5 mg dosing on Days 1-3, completed >90% cytisine dosing on Days 4-25 and complied with protocol-specified criteria.

Subject analysis set title	Pharmacokinetic Set: Cytisine 3.0 mg
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who completed all cytisine 3.0 mg dosing on Days 1-3, completed >90% cytisine dosing on Days 4-25 and complied with protocol-specified criteria.

Subject analysis set title	Pharmacodynamic Set: Cytisine 1.5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the Pharmacokinetic Set: Cytisine 1.5 mg who had an available baseline result and at least 1 on-treatment result with regards to urine cotinine, expired air CO or daily cigarette consumption and did not incur a major protocol deviation.

Subject analysis set title	Pharmacodynamic Set: Cytisine 1.5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the Pharmacokinetic Set: Cytisine 3.0 mg who had an available baseline result and at least 1 on-treatment result with regards to urine cotinine, expired air CO or daily cigarette consumption and did not incur a major protocol deviation.

Subject analysis set title	Safety Set: Cytisine 1.5 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

all randomized subjects who received at least one dose of 1.5 mg cytisine

Subject analysis set title	Safety Set: Cytisine 3.0 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

all randomized subjects who received at least one dose of 3.0 mg cytisine

Subject analysis set title	Electrocardiogram Set: Cytisine 1.5 mg
Subject analysis set type	Full analysis

Subject analysis set description:

all subjects who received at least 1 dose of cytisine, with at least 1 available baseline electrocardiogram (ECG) and at least 1 on-treatment ECG

Subject analysis set title	Electrocardiogram Set: Cytisine 3.0 mg
Subject analysis set type	Full analysis

Subject analysis set description:

all subjects who received at least 1 dose of cytisine, with at least 1 available baseline ECG and at least 1 on-treatment ECG

Primary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[1]

End point description:

End point type	Primary

End point timeframe:

after the first dose and the last dose on Day 1; after the last dose on Days 2, 3, 12, 16, 20, 24; and after the morning dose on Day 25

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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[2]	13[3]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1, first dose; n=13, 13	21.1 (± 24.8)	40.0 (± 26.8)		
Day 1, last dose; n=13, 13	33.8 (± 20.0)	81.4 (± 30.1)		
Day 2, last dose; n=13, 13	32.9 (± 22.3)	85.1 (± 20.9)		
Day 3, last dose; n=13, 13	35.9 (± 21.7)	88.1 (± 19.3)		
Day 12, last dose; n=13, 13	29.9 (± 24.9)	69.9 (± 31.5)		
Day 16, last dose; n=13, 13	23.7 (± 31.4)	50.5 (± 26.5)		
Day 20, first dose; n=12, 13	23.0 (± 22.1)	49.7 (± 30.9)		
Day 24, first dose; n=12, 13	16.0 (± 28.3)	42.0 (± 33.6)		
Day 25; n=12, 13	12.6 (± 19.4)	28.1 (± 27.4)		

Notes:

[2] - n=subjects with an assessment at given time point

[3] - n=subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Primary: Time of Occurrence of Cmax (Tmax)

End point title	Time of Occurrence of Cmax (Tmax)[4]

End point description:

End point type	Primary

End point timeframe:

after the first dose and the last dose on Day 1; after the last dose on Days 2, 3, 12, 16, 20, 24; and after the morning dose on Day 25

Notes:

[4] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[5]	13[6]		
Units: hours				
median (full range (min-max))				
Day 1, first dose; n=13, 13	0.500 (0.500 to 0.750)	0.750 (0.500 to 1.00)		
Day 1, last dose; n=13, 13	1.00 (0.00 to 2.50)	1.00 (0.00 to 2.50)		
Day 2, last dose; n=13, 13	1.00 (0.00 to 3.50)	1.00 (0.00 to 3.50)		
Day 3, last dose; n=13, 13	1.00 (0.500 to 3.00)	1.00 (0.00 to 2.03)		
Day 12, last dose; n=13, 13	1.00 (0.00 to 3.05)	1.02 (0.00 to 2.00)		
Day 16, last dose; n=13, 13	2.50 (0.00 to 4.02)	2.00 (1.00 to 6.50)		
Day 20, last dose; n=12, 13	1.50 (1.00 to 5.50)	1.00 (0.00 to 6.50)		
Day 24, last dose; n=12, 13	2.00 (1.00 to 4.00)	1.00 (1.00 to 3.00)		
Day 25; n=12, 13	2.50 (0.500 to 5.00)	2.25 (0.500 to 3.75)		

Notes:

[5] - n=subjects with an assessment at given time point

[6] - n=subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Observed Plasma Concentration (Cmin)

End point title	Minimum Observed Plasma Concentration (Cmin)[7]

End point description:

End point type	Primary

End point timeframe:

after the first dose on Days 4, 13, 17, 21 and 25

Notes:

[7] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[8]	13[9]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 4, first dose; n=13, 13	5.36 (± 47.7)	13.2 (± 27.4)		
Day 13, first dose; n=13, 13	5.16 (± 48.2)	12.6 (± 33.0)		
Day 17, first dose; n=13, 13	4.19 (± 64.7)	8.50 (± 38.3)		
Day 21, first dose; n=13, 13	3.13 (± 83.4)	6.34 (± 39.0)		
Day 25; n=12, 13	3.16 (± 188.9)	3.74 (± 42.4)		

Notes:

[8] - n=subjects with an assessment at given time point

[9] - n=subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Versus Time Curve (AUC) From Time Zero to the Last Sampling Time (AUC0-t)

End point title	Area Under the Plasma Concentration Versus Time Curve (AUC) From Time Zero to the Last Sampling Time (AUC0-t)[10]

End point description:

End point type	Primary

End point timeframe:

after the administration of the final dose of cytisine on Day 25

Notes:

[10] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[11]	13		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	67.0 (± 27.4)	185 (± 32.3)		

Notes:

[11] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Primary: Total AUC From Time Zero to Infinity (AUC0-∞)

End point title	Total AUC From Time Zero to Infinity (AUC0-∞)[12]

End point description:

End point type	Primary

End point timeframe:

after the administration of the final dose of cytisine on Day 25

Notes:

[12] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[13]	13		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	82.6 (± 30.4)	213 (± 28.0)		

Notes:

[13] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Primary: Residual Area or Percentage of Extrapolated Part for the Calculation of AUC0-∞ (%AUC)

End point title	Residual Area or Percentage of Extrapolated Part for the Calculation of AUC0-∞ (%AUC)[14]

End point description:

End point type	Primary

End point timeframe:

after the administration of the final dose of cytisine on Day 25

Notes:

[14] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[15]	13		
Units: percentage of extrapolated part				
geometric mean (geometric coefficient of variation)	18.0 (± 28.9)	11.7 (± 40.1)		

Notes:

[15] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Elimination Rate Constant (λz)

End point title	Apparent Terminal Elimination Rate Constant (λz)[16]

End point description:

End point type	Primary

End point timeframe:

after the administration of the final dose of cytisine on Day 25

Notes:

[16] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[17]	13		
Units: 1/hour				
geometric mean (geometric coefficient of variation)	0.185 (± 26.4)	0.152 (± 16.9)		

Notes:

[17] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Elimination Half-Life (t1/2)

End point title	Apparent Terminal Elimination Half-Life (t1/2)[18]

End point description:

End point type	Primary

End point timeframe:

after the administration of the final dose of cytisine on Day 25

Notes:

[18] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[19]	13		
Units: hours				
arithmetic mean (standard deviation)	3.75 (± 24.7)	4.57 (± 17.2)		

Notes:

[19] - subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Primary: Number of Cigarettes Smoked Daily During Treatment and at Day 26

End point title	Number of Cigarettes Smoked Daily During Treatment and at

	Day 26[20]

End point description:

End point type	Primary

End point timeframe:

Day 1 through Day 26

Notes:

[20] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[21]	13[22]		
Units: cigarettes smoked in the past 24 hours				
arithmetic mean (standard deviation)				
Day -1; n=13, 13	16.31 (± 3.401)	18.08 (± 5.171)		
Day 1; n=13, 13	7.31 (± 6.088)	8.77 (± 6.882)		
Day 2; n=13, 13	3.69 (± 1.437)	4.08 (± 1.801)		
Day 3; n=11, 13	4.00 (± 1.673)	4.46 (± 1.854)		
Day 4; n=13, 13	4.77 (± 2.682)	6.15 (± 3.555)		
Day 5; n=13, 13	4.08 (± 2.629)	5.69 (± 3.568)		
Day 6; n=13, 13	4.85 (± 3.826)	7.00 (± 4.778)		
Day 7; n=13, 13	4.19 (± 4.018)	4.85 (± 4.180)		
Day 8; n=13, 13	4.15 (± 3.760)	5.38 (± 4.073)		
Day 9; n=13, 13	4.77 (± 4.438)	5.08 (± 4.555)		
Day 10; n=13, 13	4.62 (± 4.234)	4.54 (± 4.557)		
Day 11; n=13, 13	3.81 (± 3.497)	4.62 (± 4.292)		
Day 12; n=13, 13	3.31 (± 3.545)	3.69 (± 3.637)		
Day 13; n=13, 13	4.15 (± 4.038)	5.00 (± 4.163)		
Day 14; n=13, 13	4.00 (± 3.786)	3.69 (± 4.535)		
Day 15; n=13, 13	4.23 (± 3.876)	3.62 (± 4.331)		
Day 16; n=13, 13	3.85 (± 3.648)	3.08 (± 3.451)		
Day 17; n=13, 13	4.00 (± 4.163)	3.77 (± 4.781)		
Day 18; n=13, 13	3.69 (± 3.903)	3.92 (± 4.873)		
Day 19; n=13, 13	3.69 (± 3.881)	3.54 (± 4.789)		
Day 20; n=12, 13	3.25 (± 3.671)	2.58 (± 3.528)		
Day 21; n=13, 13	4.54 (± 4.719)	2.92 (± 4.462)		
Day 22; n=13, 13	4.00 (± 4.163)	3.00 (± 3.958)		
Day 23; n=13, 13	4.38 (± 4.407)	2.69 (± 4.151)		
Day 24; n=13, 13	3.08 (± 2.985)	2.38 (± 3.042)		
Day 25; n=12, 13	1.17 (± 1.467)	0.85 (± 1.214)		
Day 26; n=13, 13	4.23 (± 4.206)	3.00 (± 4.778)		

Notes:

[21] - n=subjects with a valid assessment at given time point

[22] - n=subjects with a valid assessment at given time point

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Number of Cigarettes Smoked Daily up to Day 26

End point title	Change From Baseline in Number of Cigarettes Smoked Daily up to Day 26[23]

End point description:

End point type	Primary

End point timeframe:

Baseline, Day 1 through Day 26

Notes:

[23] - 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: Descriptive statistics are presented, per protocol.

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[24]	13[25]		
Units: cigarettes smoked in the past 24 hours				
arithmetic mean (standard deviation)				
Day 1; n=13, 13	-9.00 (± 5.745)	-9.31 (± 7.169)		
Day 2; n=13, 13	-12.62 (± 3.664)	-14.00 (± 5.000)		
Day 3; n=11, 13	-11.91 (± 3.885)	-13.62 (± 5.723)		
Day 4; n=13, 13	-11.54 (± 4.737)	-11.92 (± 6.144)		
Day 5; n=13, 13	-12.23 (± 4.475)	-12.38 (± 5.665)		
Day 6; n=13, 13	-11.46 (± 4.371)	-11.08 (± 7.005)		
Day 7; n=13, 13	-12.12 (± 4.718)	-13.23 (± 5.388)		
Day 8; n=13, 13	-12.15 (± 4.580)	-12.69 (± 5.391)		
Day 9; n=13, 13	-11.54 (± 5.333)	-13.00 (± 5.845)		
Day 10; n=13, 13	-11.69 (± 4.697)	-13.54 (± 5.425)		
Day 11; n=13, 13	-12.50 (± 4.173)	-13.46 (± 4.789)		
Day 12; n=13, 13	-13.00 (± 4.813)	-14.38 (± 4.992)		
Day 13; n=13, 13	-12.15 (± 4.543)	-13.08 (± 6.873)		
Day 14; n=13, 13	-12.31 (± 4.309)	-14.38 (± 6.185)		
Day 15; n=13, 13	-12.08 (± 4.212)	-14.46 (± 5.592)		
Day 16; n=13, 13	-12.46 (± 3.597)	-15.00 (± 5.083)		
Day 17; n=13, 13	-12.31 (± 4.768)	-14.31 (± 5.721)		

Day 18; n=13, 13	-12.62 (± 4.753)	-14.15 (± 6.012)		
Day 19; n=13, 13	-12.62 (± 4.556)	-14.54 (± 5.577)		
Day 20; n=12, 12	-13.17 (± 3.810)	-15.83 (± 4.569)		
Day 21; n=13, 13	-11.77 (± 5.262)	-15.15 (± 5.535)		
Day 22; n=13, 13	-12.31 (± 4.404)	-15.08 (± 5.251)		
Day 23; n=13, 13	-11.92 (± 4.873)	-15.38 (± 5.091)		
Day 24; n=13, 13	-13.23 (± 4.419)	-15.69 (± 4.461)		
Day 25; n=12, 13	-14.83 (± 3.407)	-17.23 (± 4.850)		
Day 26; n=13, 13	-12.08 (± 4.645)	-15.08 (± 4.387)		

Notes:

[24] - n=subjects with a valid assessment at given time point

[25] - n=subjects with a valid assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Expired Air CO up to Day 26

End point title	Change From Baseline in Expired Air CO up to Day 26

End point description:

End point type	Secondary

End point timeframe:

Baseline, Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[26]	13[27]		
Units: ppm				
arithmetic mean (standard deviation)				
Day 4; n=13, 13	-13.2 (± 8.34)	-13.8 (± 7.03)		
Day 13; n=13, 12	-15.3 (± 8.02)	-15.9 (± 6.84)		
Day 17; n=13, 13	-16.0 (± 7.93)	-16.2 (± 5.81)		
Day 21; n=13, 13	-16.4 (± 7.79)	-16.5 (± 6.08)		
Day 26; n=13, 13	-17.2 (± 8.33)	-17.9 (± 6.75)		

Notes:

[26] - n=subjects with an assessment at given time point

[27] - n=subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Ceased or Continued Smoking on Day 26

End point title	Number of Subjects Who Ceased or Continued Smoking on Day 26

End point description:

A status of "ceased smoking" is defined as not having smoked any cigarettes for the past 24 hours on Day 26 and having an expired CO level <10 ppm on Day 26.

End point type	Secondary

End point timeframe:

Day 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: subjects				
Ceased Smoking	5	7		
Continued Smoking	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Urine Cotinine

End point title	Change From Baseline Over Time in Urine Cotinine

End point description:

End point type	Secondary

End point timeframe:

Baseline, Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 4	-1040.8 (± 579.78)	-1339.2 (± 550.74)		
Day 13	-1010.0 (± 797.78)	-1309.3 (± 761.77)		

Day 17	-1012.1 (± 710.39)	-1405.2 (± 814.08)		
Day 21	-1095.1 (± 679.81)	-1446.3 (± 828.68)		
Day 26	-1362.2 (± 545.84)	-1640.2 (± 688.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TCQ-SF Score: Emotionality

End point title	Change From Baseline Over Time in TCQ-SF Score: Emotionality

End point description:

The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Emotionality scores may range from 3 to 21, with lower scores indicating weaker emotional signs of tobacco craving.

End point type	Secondary

End point timeframe:

Baseline (Day -1), Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 4	-5.2 (± 5.40)	-6.0 (± 5.03)		
Day 13	-4.9 (± 5.96)	-7.2 (± 4.88)		
Day 17	-5.8 (± 6.12)	-7.3 (± 5.06)		
Day 21	-5.8 (± 6.38)	-7.6 (± 5.09)		
Day 26	-5.7 (± 7.00)	-8.2 (± 4.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TCQ-SF Score: Expectancy

End point title	Change From Baseline Over Time in TCQ-SF Score: Expectancy

End point description:

The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each

item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Expectancy scores may range from 3 to 21, with lower scores indicating less positive expectations about smoking.

End point type	Secondary

End point timeframe:

Baseline (Day -1), Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[28]	13[29]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 4; n=13, 12	-3.8 (± 5.89)	-8.0 (± 6.00)		
Day 13; n=13, 13	-3.5 (± 7.83)	-8.4 (± 5.91)		
Day 17; n=13, 13	-4.7 (± 6.96)	-8.8 (± 5.82)		
Day 21; n=13, 13	-5.2 (± 6.56)	-9.2 (± 5.75)		
Day 26; n=13, 13	-6.2 (± 6.40)	-9.8 (± 6.15)		

Notes:

[28] - n=subjects with an assessment at given time point

[29] - n=subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TCQ-SF Score: Compulsivity

End point title	Change From Baseline Over Time in TCQ-SF Score: Compulsivity

End point description:

The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly agree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Compulsivity scores may range from 3 to 21, with lower scores indicating compulsion to smoke was a lesser component of tobacco craving.

End point type	Secondary

End point timeframe:

Baseline (Day -1), Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: score on a scale				

arithmetic mean (standard deviation)				
Day 4	-3.2 (± 3.18)	-3.5 (± 4.74)		
Day 13	-3.7 (± 6.56)	-4.9 (± 4.77)		
Day 17	-4.4 (± 6.32)	-5.2 (± 4.44)		
Day 21	-4.4 (± 5.49)	-5.3 (± 4.82)		
Day 26	-4.3 (± 5.94)	-5.8 (± 4.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TCQ-SF Score: Purposefulness

End point title	Change From Baseline Over Time in TCQ-SF Score: Purposefulness

End point description:

The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Purposefulness scores may range from 3 to 21, with lower scores indicating stronger ability to not smoke.

End point type	Secondary

End point timeframe:

Baseline (Day -1), Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 4	-6.5 (± 2.93)	-7.5 (± 4.99)		
Day 13	-6.6 (± 6.34)	-9.1 (± 5.45)		
Day 17	-7.6 (± 6.33)	-9.2 (± 6.09)		
Day 21	-7.8 (± 6.48)	-10.3 (± 5.65)		
Day 26	-9.0 (± 5.15)	-11.1 (± 5.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TCQ-SF Score: Total Score

End point title	Change From Baseline Over Time in TCQ-SF Score: Total Score

End point description:

The TCQ-SF is a 12-item questionnaire that assesses 4 components of tobacco craving: emotionality (3 items), expectancy (3 items), compulsivity (3 items) and purposefulness (3 items). Responses to each item are scored from 1 (strongly disagree) through 7 (strongly disagree). Component scores are defined as the sum of the scores within each component. The total score is defined as the sum of the 4 component scores. Total scores may range from 12 to 84, with lower scores indicating lower tobacco craving.

End point type	Secondary

End point timeframe:

Baseline (Day -1), Days 4, 13, 17, 21, 26

End point values	Pharmacodynamic Set: Cytisine 1.5 mg	Pharmacodynamic Set: Cytisine 1.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[30]	13[31]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 4; n=13, 12	-18.7 (± 12.88)	-26.0 (± 16.06)		
Day 13; n=13, 13	-18.7 (± 22.11)	-29.6 (± 16.58)		
Day 17; n=13, 13	-22.5 (± 22.17)	-30.5 (± 16.51)		
Day 21; n=13, 13	-23.2 (± 21.79)	-32.5 (± 16.62)		
Day 26; n=13, 13	-25.2 (± 20.55)	-34.8 (± 16.85)		

Notes:

[30] - n=subjects with an assessment at given time point

[31] - n=subjects with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Cytisine Amount Excreted in Urine Over Time (Ae0-24h)

End point title	Cytisine Amount Excreted in Urine Over Time (Ae0-24h)

End point description:

End point type	Secondary

End point timeframe:

Day 1 (6 times daily at 2-hour intervals); after the administration of the single dose of cytisine on Day 25

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: mg				
geometric mean (geometric coefficient of variation)				
Day 1	7.95 (± 14.3)	16.5 (± 12.0)		
Day 25	1.54 (± 17.4)	3.14 (± 12.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Drug Excreted in Urine (Ae%)

End point title	Percent of Drug Excreted in Urine (Ae%)

End point description:

End point type	Secondary

End point timeframe:

Day 1 (6 times daily at 2-hour intervals); after the administration of the single dose of cytisine on Day 25

End point values	Pharmacokinetic Set: Cytisine 1.5 mg	Pharmacokinetic Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: percent				
geometric mean (geometric coefficient of variation)				
Day 1	88.3 (± 14.3)	91.6 (± 12.0)		
Day 25	102 (± 17.4)	105 (± 12.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and Discontinuation of Study Drug Due to TEAEs

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and Discontinuation of Study Drug Due to TEAEs

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with the

treatment. A serious adverse event (SAE) is defined as an AE that results in any of the following: results in death; is life-threatening; requires hospitalisation or prolongs existing inpatient's hospitalisation; results in persistent or significant disability or incapacity; results in a congenital abnormality or birth defect; is an important medical event which requires medical intervention to prevent any of the above outcomes.TEAEs are defined as AEs not present prior to first administration of investigational product, or AEs present before first administration of investigational product that worsen after the participant receives the first dose of investigational product.

End point type	Secondary

End point timeframe:

From first dose of study drug through Day 26 plus 6-8 days

End point values	Safety Set: Cytisine 1.5 mg	Safety Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: subjects				
TEAEs	9	9		
Serious TEAEs	0	0		
Discontinuation of Study Drug due to TEAE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Values in Baseline in Biochemistry, Hematology, and Urinalysis

End point title	Number of Subjects With Clinically Significant Values in Baseline in Biochemistry, Hematology, and Urinalysis

End point description:

End point type	Secondary

End point timeframe:

up to Day 26

End point values	Safety Set: Cytisine 1.5 mg	Safety Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: subjects				
Biochemistry	0	0		
Hematology	0	0		
Urinalysis	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Values in Vital Signs and Physical Examinations

End point title	Number of Subjects With Clinically Significant Values in Vital Signs and Physical Examinations

End point description:

End point type	Secondary

End point timeframe:

up to Day 26

End point values	Safety Set: Cytisine 1.5 mg	Safety Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: subjects				
Vital Signs	0	0		
Physical Examinations	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes in 12-lead Electrocardiogram (ECG) Parameters

End point title	Number of Subjects With Clinically Significant Changes in 12-lead Electrocardiogram (ECG) Parameters

End point description:

End point type	Secondary

End point timeframe:

up to Day 26

End point values	Safety Set: Cytisine 1.5 mg	Safety Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Holter ECG Outlier Values

End point title	Number of Subjects With Holter ECG Outlier Values

End point description:

Based on the mean of the triplicate recordings at each time point. Increase ()/decrease () calculated from Baseline (BL), defined as the mean of all recordings taken prior to dosing on Day 1 (i.e. -30 minutes and -15 minutes). A subject with multiple occurrences of an event is counted only once per event.

End point type	Secondary

End point timeframe:

on Day 1 and Day 25 at 30 and 15 minutes prior to the first dose and 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours and 24 hours post dose

End point values	Electrocardiogram Set: Cytisine 1.5 mg	Electrocardiogram Set: Cytisine 3.0 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: subjects				
Day 1: Heart Rate <50 bpm & ≥ 25%	0	0		
Day 1: Heart Rate >100 bpm & ≥25%	1	0		
Day 1: PR Interval >200 mSec & ≥25%	0	0		
Day 1: QRS Duration >100 mSec & ≥25%	0	0		
Day 1: QT Interval >500 mSec & BL ≤500 mSec	0	0		
Day 1: QTcF Interval >500 mSec & BL ≤500 mSec	0	0		
Day 1: QTcF Interval >480 mSec & BL ≤480 mSec	0	0		
Day 1: QTcF Interval >450 mSec & BL ≤450 mSec	0	1		
Day 25: Heart Rate <50 bpm & ≥ 25%	0	0		
Day 25: Heart Rate >100 bpm & ≥25%	1	0		
Day 25: PR Interval >200 mSec & ≥25%	0	0		
Day 25: QRS Duration >100 mSec & ≥25%	0	1		

Day 25: QT Interval >500 mSec & BL ≤500 mSec	0	0		
Day 25: QTcF Interval >500 mSec & BL ≤500 mSec	0	0		
Day 25: QTcF Interval >480 mSec & BL ≤480 mSec	0	0		
Day 25: QTcF Interval >450 mSec & BL ≤450 mSec	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through Day 26 plus 6-8 days

Adverse event reporting additional description:

TEAEs are presented. TEAEs are defined as AEs not present prior to first administration of investigational product, or AEs present before first administration of investigational product that worsen after the subject receives the first dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Cytisine 1.5 mg

Reporting group description:

Multiple doses of 1.5 mg cytisine administered per 25-day schedule:
• Days 1-3 (6 times daily)
• Days 4-12 (5 times daily)
• Days 13-16 (4 times daily)
• Days 17-20 (3 times daily)
• Days 21-24 (2 times daily)
• Day 25 (Once daily)

Reporting group title	Cytisine 3.0 mg

Reporting group description:

Multiple doses of 3.0 mg cytisine administered per 25-day schedule:
• Days 1-3 (6 times daily)
• Days 4-12 (5 times daily)
• Days 13-16 (4 times daily)
• Days 17-20 (3 times daily)
• Days 21-24 (2 times daily)
• Day 25 (Once daily)

Serious adverse events	Cytisine 1.5 mg	Cytisine 3.0 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cytisine 1.5 mg	Cytisine 3.0 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)	9 / 13 (69.23%)	
Injury, poisoning and procedural complications			

Muscle strain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 13 (30.77%)	6 / 13 (46.15%)	
occurrences (all)	9	15	
Vision blurred			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Medical device site reaction			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Nausea			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Tooth loss			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sinonasal obstruction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2017	The amendment was issued in line with recommendations made by the MHRA prior to authorization of the study. The recommendations included: Amendment of the inclusion criteria to remove subjects who used statins, thyroxine and antihypertensive drugs. Clarification that other medications listed in the Tabex SmPC (tuberculostatitics, cholinomimetics or anticholinesterase medicinal products, statins, or antihypertensive medicinal products) were not to be taken during the study and breast feeding was to be exclusionary. Additional vital sign assessments to be performed near expected Cmax while in the Clinical Unit and that ECGs may be performed at any time during study, if clinically indicated.
08 November 2017	This study-conduct change was issued to create adverts for use on Facebook, Google PPC and Instagram and in posters in order to aid recruitment for the study, particularly focusing on subjects aged >65. The study-conduct change was approved by the REC on 16 November 2017.
16 January 2018	This study-conduct change was issued to use additional Participant Identification Centers (Llandaff North Medical Centre, Llanrumney Medical Group) to aid the recruitment of subjects (aged >65) who smoked at least 10 cigarettes each day and would like to quit smoking. An application was also submitted to Research Permissions Wales for a study wide governance review. The study-conduct change was approved by REC on 16 February 2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported