Clinical trial results:
PHARMACODYNAMIC EFFECTS OF NICOTINE MOUTH SPRAY AND CYTISINE TABLET. A STUDY IN HEALTHY SMOKERS

Summary

EudraCT number	2016-001267-36
Trial protocol	SE
Global end of trial date	07 October 2016

Results information

Result version number	v1 (current)
This version publication date	26 July 2017
First version publication date	26 July 2017

Trial information

Trial identification

Sponsor protocol code	CO-160310091324-SCCT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	McNeil AB
Sponsor organisation address	251 09, Helsingborg, Sweden, Box 941
Public contact	Global Regulatory Affairs OTC Hsbg, McNeil AB, 46 42288734, GRAREGH@its.jnj.com
Scientific contact	Global Regulatory Affairs OTC Hsbg, McNeil AB, 46 42288734, GRAREGH@its.jnj.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	07 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare oromucosal nicotine spray (ONS), two sprays of 1 milligram (mg) nicotine, and one Tabex tablet of 1.5 mg cytisine after 12 hours of overnight abstinence with respect to reduction of urges to smoke during the first 5 minutes after start of treatment and to compare the two treatments with respect to the urges-to-smoke scores at 30, 45, and 60 seconds, 3 and 5 minutes versus baseline.

Protection of trial subjects:

Safety was evaluated by monitoring of adverse events (AEs) throughout study and, vital signs measurements, physical and other observational examinations was evaluated during screening phase.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2016
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	Sweden: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	61
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 27 June 2016 to 07 October 2016 in Sweden.

Pre-assignment

Screening details:

A total of 61 subjects were enrolled in study out of which 28 were males and 33 were females.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1: Nicorette Oromucosal Nicotine Spray (ONS), Tabex

Arm description:

Subjects received nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A followed by tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B. Each treatment was separated by wash-out periods of at least 36 hours.

Arm type	Experimental
Investigational medicinal product name	Tabex
Investigational medicinal product code	SUB31171
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B.

Investigational medicinal product name	Nicorette Pepparmint 1 mg/spray
Investigational medicinal product code	SUB14645MIG
Other name	
Pharmaceutical forms	Oromucosal spray, solution
Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received nicorette peppermint oromucosal spray 2 mg as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A.

Arm title	Sequence 2: Tabex, Nicorette ONS

Arm description:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B followed by nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A. Each treatment was separated by wash-out periods of at least 36 hours.

Arm type	Experimental
Investigational medicinal product name	Tabex
Investigational medicinal product code	SUB31171
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B.

Investigational medicinal product name	Nicorette Pepparmint 1 mg/spray
Investigational medicinal product code	SUB14645MIG
Other name	
Pharmaceutical forms	Oromucosal spray, solution
Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received nicorette peppermint oromucosal spray 2 mg as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A.

Number of subjects in period 1	Sequence 1: Nicorette Oromucosal Nicotine Spray (ONS), Tabex	Sequence 2: Tabex, Nicorette ONS
Started	31	30
Completed	31	30

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1: Nicorette ONS, Tabex

Arm description:

Subjects received nicorette peppermint oromucosal spray 2 mg as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A followed by tabex tablet 1.5 mg orally with 150 mL of ambient temperature water as treatment B. Each treatment was separated by wash-out periods of at least 36 hours.

Arm type	Experimental
Investigational medicinal product name	Tabex
Investigational medicinal product code	SUB31171
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B.

Investigational medicinal product name	Nicorette Pepparmint 1 mg/spray
Investigational medicinal product code	SUB14645MIG
Other name	
Pharmaceutical forms	Oromucosal spray, solution

Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received nicorette peppermint oromucosal spray 2 mg as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A.

Arm title	Sequence 2: Tabex, Nicorette ONS

Arm description:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B followed by nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A. Each treatment was separated by wash-out periods of at least 36 hours.

Arm type	Experimental
Investigational medicinal product name	Nicorette Pepparmint 1 mg/spray
Investigational medicinal product code	SUB14645MIG
Other name	
Pharmaceutical forms	Oromucosal spray, solution
Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received nicorette peppermint oromucosal spray 2 mg as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A.

Investigational medicinal product name	Tabex
Investigational medicinal product code	SUB31171
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B.

Number of subjects in period 2	Sequence 1: Nicorette ONS, Tabex	Sequence 2: Tabex, Nicorette ONS
Started	31	30
Completed	26	28
Not completed	5	2
Consent withdrawn by subject	-	1
Other	2	-
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1: Nicorette Oromucosal Nicotine Spray (ONS), Tabex

Reporting group description:

Subjects received nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A followed by tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B. Each treatment was separated by wash-out periods of at least 36 hours.

Reporting group title	Sequence 2: Tabex, Nicorette ONS

Reporting group description:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B followed by nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A. Each treatment was separated by wash-out periods of at least 36 hours.

Reporting group values	Sequence 1: Nicorette Oromucosal Nicotine Spray (ONS), Tabex	Sequence 2: Tabex, Nicorette ONS	Total
Number of subjects	31	30	61
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	30	61
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	33	31.6	
standard deviation	± 10.97	± 10.85	-
Title for Gender Units: subjects			
Female	15	18	33
Male	16	12	28

End points

End points reporting groups

Reporting group title	Sequence 1: Nicorette Oromucosal Nicotine Spray (ONS), Tabex

Reporting group description:

Subjects received nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A followed by tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B. Each treatment was separated by wash-out periods of at least 36 hours.

Reporting group title	Sequence 2: Tabex, Nicorette ONS

Reporting group description:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B followed by nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A. Each treatment was separated by wash-out periods of at least 36 hours.

Reporting group title	Sequence 1: Nicorette ONS, Tabex

Reporting group description:

Subjects received nicorette peppermint oromucosal spray 2 mg as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A followed by tabex tablet 1.5 mg orally with 150 mL of ambient temperature water as treatment B. Each treatment was separated by wash-out periods of at least 36 hours.

Reporting group title	Sequence 2: Tabex, Nicorette ONS

Reporting group description:

Subjects received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water as treatment B followed by nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits as treatment A. Each treatment was separated by wash-out periods of at least 36 hours.

Subject analysis set title	Nicorette ONS (Treatment A)
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects with any efficacy assessments and received nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits.

Subject analysis set title	Tabex (Treatment B)
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects with any efficacy assessments and received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water.

Subject analysis set title	ONS Versus (vs.) Tabex
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects with any efficacy assessments and involved in comparisons of ONS vs. Tabex with respect to time to reduce craving score.

Primary: Average Change in Visual Analog Scale (VAS) Craving Score Compared to Baseline

End point title	Average Change in Visual Analog Scale (VAS) Craving Score Compared to Baseline

End point description:

Urges to smoke was scored on a 100 millimeter (mm) VAS before treatment and then repeatedly during 2 hours. Baseline urges to smoke was also rated using a 4- grade scale. On the scale, 0 corresponds to "no urge to smoke" and 100 mm corresponds to "extreme urge to smoke". Full analysis set population included all randomized subjects with any efficacy assessments.

End point type	Primary

End point timeframe:

Baseline, 30 seconds (sec), 45 sec, 1 minute (min), 3 min and 5 min

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: millimeter				
arithmetic mean (standard deviation)				
30 seconds (sec)	-8 (± 9.8)	-0.8 (± 4.9)		
45 sec	-11.8 (± 14.1)	-1 (± 6.1)		
1 minute (min)	-14.7 (± 16.5)	-1.3 (± 6)		
3 min	-23 (± 21)	-3.8 (± 9.7)		
5 min	-26.3 (± 22)	-5.8 (± 12)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis was done for average change in VAS craving score compared to baseline up to 30 seconds. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Tabex (Treatment B) v Nicorette ONS (Treatment A)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	-4.2
Variability estimate	Standard error of the mean
Dispersion value	1.4

Notes:

[1] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis was done for average change in VAS craving score compared to baseline up to 45 seconds. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	-6.5
Variability estimate	Standard error of the mean
Dispersion value	2

Notes:

[2] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis was done for average change in VAS craving score compared to baseline up to 1 minute. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Tabex (Treatment B) v Nicorette ONS (Treatment A)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-13.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	-8.6
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[3] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis was done for average change in VAS craving score compared to baseline up to 3 minutes. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	-13.2
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[4] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Analysis was done for average change in VAS craving score compared to baseline up to 5 minutes. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.3
upper limit	-14.3
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[5] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Primary: Change in VAS Craving Score Compared to Baseline

End point title	Change in VAS Craving Score Compared to Baseline

End point description:

Urges to smoke was scored on a 100 millimeter (mm) VAS before treatment and then repeatedly during 2 hours. Baseline urges to smoke was also rated using a 4- grade scale. On the scale, 0 corresponds to "no urge to smoke" and 100 mm corresponds to "extreme urge to smoke". Full analysis set population included all randomized subjects with any efficacy assessments.

End point type	Primary

End point timeframe:

Baseline, 30 seconds (sec), 45 sec, 1 minute (min), 3 min and 5 min

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: millimeter				
arithmetic mean (standard deviation)				
30 sec	-15.9 (± 19.5)	-1.5 (± 9.7)		
45 sec	-21.9 (± 23.9)	-1.6 (± 8.2)		
1 min	-24.5 (± 24.2)	-2.8 (± 10.6)		
3 min	-30.3 (± 25.9)	-6.8 (± 14.6)		
5 min	-34.3 (± 26)	-10.7 (± 18)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis was done for change in VAS craving score compared to baseline at 30 seconds. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	-8.3
Variability estimate	Standard error of the mean
Dispersion value	2.8

Notes:

[6] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis was done for change in VAS craving score compared to baseline at 45 seconds. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.4
upper limit	-13.5
Variability estimate	Standard error of the mean
Dispersion value	3.2

Notes:

[7] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis was done for change in VAS craving score compared to baseline at 1 minute. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.7
upper limit	-14.7
Variability estimate	Standard error of the mean
Dispersion value	3.2

Notes:

[8] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis was done for change in VAS craving score compared to baseline at 3 minutes. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-22.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.7
upper limit	-16.2
Variability estimate	Standard error of the mean
Dispersion value	3.1

Notes:

[9] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Analysis was done for change in VAS craving score compared to baseline at 5 minutes. Treatment comparison was based on a mixed linear model including sequence, treatment and period as fixed effects and subject, nested within sequence, as random effect. Additionally, the baseline urges-to-smoke score at time zero, was calculated as an average of the three pretreatment urge assessments, was included as a co-varying fixed effect.

Comparison groups	Nicorette ONS (Treatment A) v Tabex (Treatment B)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-22.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.4
upper limit	-16.1
Variability estimate	Standard error of the mean
Dispersion value	3.1

Notes:

[10] - 58 subjects from treatment A and 56 subjects from treatment B were involved in the analysis (Cross over design with random model). In total 61 unique subjects were included in the analysis.

Secondary: Time to a 25 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point title	Time to a 25 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point description:

Kaplan-Meier survival estimates method was used for the time to 25% reduction in urges to smoke. Full analysis set population included all randomized subjects with any efficacy assessments. Here '99999' represents that no estimate was available for median and confidence interval for this specific outcome result.

End point type	Secondary

End point timeframe:

up to 2 hours

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: Minutes				
median (confidence interval 95%)				
25 % quartiles	0.245 (0.195 to 0.356)	3.085 (1.274 to 7.871)		
50 % quartiles	0.707 (0.378 to 2.142)	16.51 (7.871 to 44.46)		
75 % quartiles	3.183 (2.142 to 12.97)	99999 (69.37 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rating of Withdrawal Symptoms

End point title	Rating of Withdrawal Symptoms

End point description:

The four negative affect related items of the Minnesota Nicotine Withdrawal Scale (MNWS) were used. These include depressed mood, irritability, anxiety, and difficulty concentrating. Each was rated on a 5-grade scale; 0 – not present, 1 – slight, 2 – mild, 3 – moderate, 4 – severe within 10 minutes before treatment and at 5 and 30 minutes, as well as 1 and 2 hours after treatment. Full analysis set population included all randomized subjects with any efficacy assessments.

End point type	Secondary

End point timeframe:

Baseline, 5 min, 30 min, 1 hour and 2 hour

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	56		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Depressed Mood: Baseline	1.6 (± 1.1)	1.6 (± 1)		
Depressed Mood: 5 min	1.1 (± 1)	1.1 (± 0.9)		
Depressed Mood: 30 min	1 (± 1)	0.9 (± 1)		
Depressed Mood: 1 hour	0.9 (± 1)	0.8 (± 0.9)		
Depressed Mood: 2 hour	0.9 (± 0.9)	0.9 (± 1)		
Irritability: Baseline	1.8 (± 1.2)	1.7 (± 1.2)		
Irritability: 5 min	1.3 (± 1.1)	1.3 (± 1.1)		
Irritability: 30 min	1 (± 1)	1.1 (± 1.1)		

Irritability: 1 hour	0.9 (± 1)	1.1 (± 1.1)		
Irritability: 2 hour	1.1 (± 1)	1 (± 1)		
Anxiety: Baseline	1.4 (± 1.1)	1.2 (± 1.1)		
Anxiety: 5 min	0.9 (± 0.9)	0.8 (± 0.9)		
Anxiety: 30 min	0.8 (± 0.9)	0.8 (± 0.8)		
Anxiety: 1 hour	0.8 (± 0.9)	0.9 (± 1)		
Anxiety: 2 hour	0.9 (± 1)	0.9 (± 1)		
Difficulty Concentrating: Baseline	1.8 (± 1.2)	1.6 (± 1.2)		
Difficulty Concentrating: 5 min	1.2 (± 1.1)	1.3 (± 1.1)		
Difficulty Concentrating: 30 min	1.2 (± 1)	1.2 (± 1)		
Difficulty Concentrating: 1 hour	1.1 (± 1)	1.2 (± 1.1)		
Difficulty Concentrating: 2 hour	1.3 (± 1.1)	1.2 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Preference of Treatment With Respect to Craving Relief

End point title	Percentage of Subjects in Preference of Treatment With Respect to Craving Relief

End point description:

Product preference was decided by asking the question at the end of the last treatment visit that which of the two treatments do you prefer with regards to relief of urges to smoke?. Full analysis set population included all randomized subjects with any efficacy assessments.

End point type	Secondary

End point timeframe:

End of visit 2

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	56		
Units: percentage of subjects				
number (not applicable)	64.8	35.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events

End point title	Number of Subjects With Treatment Emergent Adverse Events

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment-emergent were events between administration of study drug and up to end of visit 2 that were absent before treatment or that

worsened relative to pretreatment state. All subjects who received at least one dose of treatment were included in the safety analysis
set.

End point type	Secondary
End point timeframe:	
End of Visit 2	

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	56		
Units: Subjects	52	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to a 50 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point title	Time to a 50 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score
End point description:	
Kaplan-Meier survival estimates method was used for the time to 50% reduction in urges to smoke. Full analysis set population included all randomized subjects with any efficacy assessments. Here '99999' represents that no estimate was available for median and confidence interval for this specific outcome result.	
End point type	Secondary
End point timeframe:	
up to 2 hours	

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: Minutes				
median (confidence interval 95%)				
25% quartiles	0.491 (0.39 to 0.794)	11.69 (5.2 to 19.48)		
50% quartiles	4.364 (0.806 to 8.361)	54.01 (19.48 to 99999)		
75% quartiles	68.19 (8.361 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to a 75 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point title	Time to a 75 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point description:

Kaplan-Meier survival estimates method was used for the time to 25% reduction in urges to smoke. Full analysis set population included all randomized subjects with any efficacy assessments. Here '99999' represents that no estimate was available for median and confidence interval for this specific outcome result.

End point type	Secondary

End point timeframe:

up to 2 hours

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: Minutes				
median (confidence interval 95%)				
25% quartiles	0.876 (0.585 to 2.885)	75.52 (23.12 to 99999)		
50% quartiles	33.17 (9.868 to 99999)	99999 (99999 to 99999)		
75% quartiles	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to a 90 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point title	Time to a 90 Percent (%) Reduction From Baseline Intensity of Urges to Smoke Score

End point description:

Kaplan-Meier survival estimates method was used for the time to 90% reduction in urges to smoke. Full analysis set population included all randomized subjects with any efficacy assessments. Here '99999' represents that no estimate was available for median and confidence interval for this specific outcome result.

End point type	Secondary

End point timeframe:

up to 2 hours

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: Minutes				
median (confidence interval 95%)				
25% quartiles	3.218 (0.785 to 99999)	99999 (74.53 to 99999)		
50% quartiles	99999 (99999 to 99999)	99999 (99999 to 99999)		
75% quartiles	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Attaining 25%, 50%, 75%, and 90% Reduced Craving Score Compared to Baseline

End point title	Percentage of Subjects Attaining 25%, 50%, 75%, and 90% Reduced Craving Score Compared to Baseline
End point description:	
Full analysis set population included all randomized subjects with any efficacy assessments.	
End point type	Secondary
End point timeframe:	
upto 2 hours	

End point values	Nicorette ONS (Treatment A)	Tabex (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	56		
Units: Percentage of subjects				
number (not applicable)				
25% Reduction (30 sec)	43.1	5.4		
25% Reduction (45 sec)	53.4	8.9		
25% Reduction (1 min)	58.6	10.7		
25% Reduction (3 min)	72.9	23.2		
25% Reduction (5 min)	81.4	32.1		
25% Reduction (10 min)	83.1	39.3		
50% Reduction (30 sec)	27.6	1.8		
50% Reduction (45 sec)	32.8	1.8		
50% Reduction (1 min)	41.4	3.6		
50% Reduction (3 min)	47.5	5.4		
50% Reduction (5 min)	54.2	12.5		
50% Reduction (10 min)	64.4	19.6		
75% Reduction (30 sec)	6.9	1.8		
75% Reduction (45 sec)	24.1	1.8		
75% Reduction (1 min)	25.9	1.8		

75% Reduction (3 min)	37.3	3.6		
75% Reduction (5 min)	37.3	3.6		
75% Reduction (10 min)	39	5.4		
90% Reduction (30 sec)	0	1.8		
90% Reduction (45 sec)	12.1	1.8		
90% Reduction (1 min)	15.5	1.8		
90% Reduction (3 min)	22	1.8		
90% Reduction (5 min)	30.5	1.8		
90% Reduction (10 min)	30.5	3.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Attaining 25% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point title	Percentage of Subjects Attaining 25% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point description:

For the outcome classification in terms of Success or Failure in a given time frame the first outcome was the outcome during treatment with ONS 2 mg whereas the second outcome refers to treatment with Tabex

End point type	Secondary

End point timeframe:

upto 2 hours

End point values	ONS Versus (vs.) Tabex			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percentage of subjects				
number (not applicable)				
0-30 sec (Fail, Fail)	29			
0-30 sec (Success, Fail)	21			
0-30 sec (Success, Success)	3			
0-45 sec (Fail, Fail)	24			
0-45 sec (Success, Fail)	24			
0-45 sec (Success, Success)	5			
0-1 min (Fail, Fail)	22			
0-1 min (Success, Fail)	25			
0-1 min (Success, Success)	6			
0-3 min (Fail, Fail)	15			
0-3 min (Success, Fail)	27			
0-3 min (Success, Success)	12			
0-5 min (Fail, Fail)	10			
0-5 min (Fail, Success)	1			
0-5 min (Success, Fail)	27			
0-5 min (Success, Success)	16			

0-10 min (Fail, Fail)	9			
0-10 min (Fail, Success)	1			
0-10 min (Success, Fail)	24			
0-10 min (Success, Success)	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Attaining 50% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point title	Percentage of Subjects Attaining 50% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point description:

For the outcome classification in terms of Success or Failure in a given time frame the first outcome was the outcome during treatment with ONS 2 mg whereas the second outcome refers to treatment with Tabex. Full analysis set population included all randomized subjects with any efficacy assessments.

End point type	Secondary

End point timeframe:

up to 2 hours

End point values	ONS Versus (vs.) Tabex			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: percentage of subjects				
number (not applicable)				
0-30 sec (Fail, Fail)	38			
0-30 sec (Success, Fail)	14			
0-30 sec (Success, Success)	1			
0-45 sec (Fail, Fail)	35			
0-45 sec (Success, Fail)	17			
0-45 sec (Success, Success)	1			
0-1 min (Fail, Fail)	31			
0-1 min (Success, Fail)	20			
0-1 min (Success, Success)	2			
0-3 min (Fail, Fail)	28			
0-3 min (Success, Fail)	23			
0-3 min (Success, Success)	3			
0-5 min (Fail, Fail)	23			
0-5 min (Fail, Success)	1			
0-5 min (Success, Fail)	24			
0-5 min (Success, Success)	6			
0-10 min (Fail, Fail)	18			
0-10 min (Fail, Success)	1			
0-10 min (Success, Fail)	26			
0-10 min (Success, Success)	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Attaining 75% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point title	Percentage of Subjects Attaining 75% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point description:

For the outcome classification in terms of Success or Failure in a given time frame the first outcome was the outcome during treatment with ONS 2 mg whereas the second outcome refers to treatment with Tabex. Full analysis set population included all randomized subjects with any efficacy assessments.

End point type	Secondary

End point timeframe:

up to 2 hours

End point values	ONS Versus (vs.) Tabex			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: percentage of subjects				
number (not applicable)				
0-30 sec (Fail, Fail)	48			
0-30 sec (Success, Fail)	1			
0-30 sec (Success, Success)	4			
0-45 sec (Fail, Fail)	40			
0-45 sec (Success, Fail)	12			
0-45 sec (Success, Success)	1			
0-1 min (Fail, Fail)	39			
0-1 min (Success, Fail)	13			
0-1 min (Success, Success)	1			
0-3 min (Fail, Fail)	34			
0-3 min (Success, Fail)	18			
0-3 min (Success, Success)	2			
0-5 min (Fail, Fail)	34			
0-5 min (Success, Fail)	18			
0-5 min (Success, Success)	2			
0-10 min (Fail, Fail)	32			
0-10 min (Fail, Success)	1			
0-10 min (Success, Fail)	19			
0-10 min (Success, Success)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Attaining 90% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point title	Percentage of Subjects Attaining 90% Reduced Craving Score Compared to Baseline in Comparisons of ONS vs. Tabex

End point description:

For the outcome classification in terms of Success or Failure in a given time frame the first outcome was the outcome during treatment with ONS 2 mg whereas the second outcome refers to treatment with Tabex.

End point type	Secondary

End point timeframe:

upto 2 hours

End point values	ONS Versus (vs.) Tabex			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percentage of subjects				
number (not applicable)				
0-30 sec (Fail, Fail)	52			
0-30 sec (Fail, Success)	1			
0-45 sec (Fail, Fail)	46			
0-45 sec (Success, Fail)	6			
0-45 sec (Success, Success)	1			
0-1 min (Fail, Fail)	45			
0-1 min (Success, Fail)	7			
0-1 min (Success, Success)	1			
0-3 min (Fail, Fail)	42			
0-3 min (Success, Fail)	11			
0-3 min (Success, Success)	1			
0-5 min (Fail, Fail)	37			
0-5 min (Success, Fail)	16			
0-5 min (Success, Success)	1			
0-10 min (Fail, Fail)	36			
0-10 min (Fail, Success)	1			
0-10 min (Success, Fail)	16			
0-10 min (Success, Success)	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening up to end of treatment visit 2	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Nicorette ONS (Treatment A)
Reporting group description:	
All randomized subjects with any efficacy assessments and received nicorette peppermint oromucosal spray 2 milligram (mg) as two consecutive sprays of unit dose of 1 mg at two separate visits.	
Reporting group title	Tabex (Treatment B)
Reporting group description:	
All randomized subjects with any efficacy assessments and received tabex tablet 1.5 mg orally with 150 milliliter (mL) of ambient temperature water.	

Serious adverse events	Nicorette ONS (Treatment A)	Tabex (Treatment B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Nicorette ONS (Treatment A)	Tabex (Treatment B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 59 (88.14%)	9 / 56 (16.07%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 59 (3.39%)	4 / 56 (7.14%)	
occurrences (all)	2	5	
Eye disorders			
Lacrimation Increased			
subjects affected / exposed	12 / 59 (20.34%)	0 / 56 (0.00%)	
occurrences (all)	12	0	
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	4 / 59 (6.78%)	0 / 56 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	13 / 59 (22.03%)	2 / 56 (3.57%)	
occurrences (all)	14	2	
Oral Discomfort			
subjects affected / exposed	10 / 59 (16.95%)	0 / 56 (0.00%)	
occurrences (all)	10	0	
Salivary Hypersecretion			
subjects affected / exposed	11 / 59 (18.64%)	0 / 56 (0.00%)	
occurrences (all)	11	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 59 (13.56%)	0 / 56 (0.00%)	
occurrences (all)	8	0	
Hiccups			
subjects affected / exposed	16 / 59 (27.12%)	0 / 56 (0.00%)	
occurrences (all)	16	0	
Throat Irritation			
subjects affected / exposed	19 / 59 (32.20%)	1 / 56 (1.79%)	
occurrences (all)	19	1	
Throat Tightness			
subjects affected / exposed	5 / 59 (8.47%)	1 / 56 (1.79%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 59 (5.08%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Pruritus			
subjects affected / exposed	0 / 59 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	3	
Psychiatric disorders			
Hypervigilance			
subjects affected / exposed	3 / 59 (5.08%)	1 / 56 (1.79%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2016	Amendment included the changes/addition of procedure and texts in following sections; Independent ethics committee, Ethical conduct of the study; Regulatory authority, Risk benefit evaluation, Rationale, Previous and concomitant medications, Determination of sample size, Analysis of primary efficacy endpoints, Study monitoring, Case report forms / Electronic data capture and list of references.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported