



Clinical trial results:

Randomised, double-blind, placebo-controlled trial evaluating the effects of naltrexone hydrochloride nasal spray on alcohol consumption in Alcohol Use Disorder

Summary

EudraCT number	2019-002859-42
Trial protocol	GB HU
Global end of trial date	14 February 2023

Results information

Result version number	v1 (current)
This version publication date	16 March 2024
First version publication date	16 March 2024
Summary attachment (see zip file)	Clinical Study Report Synopsis (20240212 Clinical Study Report Synopsis AUD001.pdf)

Trial information

Trial identification

Sponsor protocol code	OPNT002-AUD-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Opiant Pharmaceuticals
Sponsor organisation address	233 Wilshire Blvd., Suite 280, Santa Monica, United States, CA 90401
Public contact	Global Director Clinical Development, Indivior Inc., +1 804-594-4488, trialdisclosure@indivior.com
Scientific contact	Global Director Clinical Development, Indivior Inc., +1 804-594-4488, trialdisclosure@indivior.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	01 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2023
Global end of trial reached?	Yes
Global end of trial date	14 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether treatment with naltrexone hydrochloride nasal spray reduces drinking in patients with alcohol use disorder

Protection of trial subjects:

Taking blood samples may cause bruising and discomfort and a risk of infection or blood clots at the site of the blood draw. The blood samples were assessed for a haematology and biochemistry panel to monitor changes in patients' health. Blood samples were taken by trained site personnel.

Patients were informed of all of the risks in the participant information sheet and were asked to notify their study doctor or study staff should they experience any side effects during the study. Patients were monitored throughout the study in order to minimise risks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2022
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	Poland: 125
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Bulgaria: 108
Country: Number of subjects enrolled	Hungary: 37
Worldwide total number of subjects	306
EEA total number of subjects	270

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)	285
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from the full range of treatment services available to these subjects, directly or through advertisements. Subjects completed a telephone or in person, Screening assessment to ascertain eligibility, type and stage of illness, current medication, and treatment.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	365 ^[1]
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Number of subjects completed	306
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 59
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of patients that started the pre-assignment period are the total patients screened. The worldwide number is the number of patients randomised. Some patients screen failed. This accounts for the discrepancy.

Period 1

Period 1 title	Period 1 - week 1-8
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Is this the baseline period?	Yes
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Allocation method	Randomised - controlled
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Blinding used	Double blind
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Roles blinded	Subject, Investigator, Monitor, Data analyst
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Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description: -

Arm type	Placebo
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Investigational medicinal product name	Placebo nasal spray
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Nasal spray
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Routes of administration	Intranasal use
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Dosage and administration details:

Placebo (one spray of 0.1 ml of the placebo formulation), one spray in one nostril once daily

Arm title	Naltrexone 12
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	Naltrexone hydrochloride nasal spray 12mg
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Nasal spray
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Routes of administration	Intranasal use
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Dosage and administration details:

12 mg/ml (1.2 mg: one spray of 0.1 ml of the 12 mg/ml formulation), one spray in one nostril once daily

Arm title	Naltrexone 30
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Naltrexone hydrochloride nasal spray 30mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

30 mg/ml (3 mg: one spray of 0.1 ml of the 30 mg/ml formulation), one spray in one nostril once daily

Number of subjects in period 1	Placebo	Naltrexone 12	Naltrexone 30
Started	206	47	53
Completed	187	41	46
Not completed	19	6	7
Adverse event, serious fatal	-	1	-
Physician decision	2	-	-
Adverse event, non-fatal	2	-	1
Technical problems	-	-	1
Lost to follow-up	2	1	1
Subject/guardian decision	6	3	2
Protocol deviation	7	1	2

Period 2

Period 2 title	Period 2 - week 9-16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Non-responder Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Placebo (one spray of 0.1 ml of the placebo formulation), one spray in one nostril once daily

Arm title	Placebo Non-responder Naltrexone 12
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Naltrexone hydrochloride nasal spray 12mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use
Dosage and administration details:	
12 mg/ml (1.2 mg: one spray of 0.1 ml of the 12 mg/ml formulation), one spray in one nostril once daily	
Arm title	Placebo Non-responder Naltrexone 30
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Naltrexone hydrochloride nasal spray 30mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use
Dosage and administration details:	
30 mg/ml (3 mg: one spray of 0.1 ml of the 30 mg/ml formulation), one spray in one nostril once daily	
Arm title	Naltrexone 12
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Naltrexone hydrochloride nasal spray 12mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use
Dosage and administration details:	
12 mg/ml (1.2 mg: one spray of 0.1 ml of the 12 mg/ml formulation), one spray in one nostril once daily	
Arm title	Naltrexone 30
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Naltrexone hydrochloride nasal spray 30mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use
Dosage and administration details:	
30 mg/ml (3 mg: one spray of 0.1 ml of the 30 mg/ml formulation), one spray in one nostril once daily	
Arm title	Placebo Responder Placebo
Arm description: -	
Arm type	Placebo

Investigational medicinal product name	Placebo nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Placebo (one spray of 0.1 ml of the placebo formulation), one spray in one nostril once daily

Number of subjects in period 2	Placebo Non-responder Placebo	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30
Started	23	34	30
Completed	20	28	28
Not completed	3	6	2
Physician decision	-	2	-
Study terminated by Sponsor	-	1	-
Technical problems	1	-	-
Adverse event, non-fatal	-	-	1
Lost to follow-up	-	2	-
Subject/guardian decision	2	-	1
Protocol deviation	-	1	-

Number of subjects in period 2	Naltrexone 12	Naltrexone 30	Placebo Responder Placebo
Started	41	46	100
Completed	37	42	92
Not completed	4	4	8
Physician decision	-	-	-
Study terminated by Sponsor	-	-	-
Technical problems	-	-	-
Adverse event, non-fatal	1	-	2
Lost to follow-up	1	-	2
Subject/guardian decision	1	3	4
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Naltrexone 12
Reporting group description: -	
Reporting group title	Naltrexone 30
Reporting group description: -	

Reporting group values	Placebo	Naltrexone 12	Naltrexone 30
Number of subjects	206	47	53
Age categorical			
Units: Subjects			
Adults (18-64 years)	191	45	49
From 65-84 years	15	2	4
Age continuous			
Units: years			
arithmetic mean	47.4	46.4	45.7
standard deviation	± 11.4	± 10.62	± 11.05
Gender categorical			
Units: Subjects			
Female	55	7	11
Male	151	40	42
Childbearing status			
Units: Subjects			
Able to bear children	30	2	6
Oophorectomy	0	1	0
Post Menopausal	22	4	5
Sterile (of childbearing age)	3	0	0
Premenarche	0	0	0
N/A - Male	151	40	42
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	205	47	53
Other	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	206	47	53
Unknown	0	0	0
BMI			
Units: kg/m ²			
arithmetic mean	26.23	27.13	27.48

standard deviation	± 4.162	± 4.146	± 4.706
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Reporting group values	Total		
Number of subjects	306		
Age categorical Units: Subjects			
Adults (18-64 years)	285		
From 65-84 years	21		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	73		
Male	233		
Childbearing status Units: Subjects			
Able to bear children	38		
Oophorectomy	1		
Post Menopausal	31		
Sterile (of childbearing age)	3		
Premenarche	0		
N/A - Male	233		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Black or African American	0		
Native Hawaiian or Other Pacific Islander	0		
White	305		
Other	0		
Ethnicity Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	306		
Unknown	0		
BMI Units: kg/m2 arithmetic mean standard deviation	-		

Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set consists of all randomised subjects who have at least one dose of IMP. Safety

Analysis Sets included all subjects treated in each stage according to their actual treatment group.

Subject analysis set title	ITT I Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT I Analysis Set consists of all subjects randomised in Stage I.

Subject analysis set title	ITT II Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT II Analysis Set is a subset of ITT I and consists of only the re randomised subjects, Stage I placebo nonresponders

Reporting group values	Safety Analysis Set	ITT I Analysis Set	ITT II Analysis Set
Number of subjects	306	306	87
Age categorical Units: Subjects			
Adults (18-64 years)	285	285	
From 65-84 years	21	21	
Age continuous Units: years			
arithmetic mean	47	47	46.4
standard deviation	± 11.21	± 11.21	± 10.67
Gender categorical Units: Subjects			
Female	73	73	18
Male	233	233	69
Childbearing status Units: Subjects			
Able to bear children	38	38	9
Oophorectomy	1	1	0
Post Menopausal	31	31	8
Sterile (of childbearing age)	3	3	1
Premenarche	0	0	0
N/A - Male	233	233	69
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	305	305	87
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	306	306	87
Unknown	0	0	0
BMI Units: kg/m2			
arithmetic mean	26.58	26.58	26.34
standard deviation	± 4.276	± 4.276	± 4.09

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Naltrexone 12
Reporting group description: -	
Reporting group title	Naltrexone 30
Reporting group description: -	
Reporting group title	Placebo Non-responder Placebo
Reporting group description: -	
Reporting group title	Placebo Non-responder Naltrexone 12
Reporting group description: -	
Reporting group title	Placebo Non-responder Naltrexone 30
Reporting group description: -	
Reporting group title	Naltrexone 12
Reporting group description: -	
Reporting group title	Naltrexone 30
Reporting group description: -	
Reporting group title	Placebo Responder Placebo
Reporting group description: -	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set consists of all randomised subjects who have at least one dose of IMP. Safety Analysis Sets included all subjects treated in each stage according to their actual treatment group.	
Subject analysis set title	ITT I Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT I Analysis Set consists of all subjects randomised in Stage I.	
Subject analysis set title	ITT II Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT II Analysis Set is a subset of ITT I and consists of only the re randomised subjects, Stage I placebo nonresponders	

Primary: 2-level reduction in WHO Drinking Risk Level

End point title	2-level reduction in WHO Drinking Risk Level
End point description:	
The proportion of subjects who show at least a 2-level reduction in WHO Drinking Risk Level from Baseline to end of treatment (EOT) (as evaluated in the 28 days prior to the Baseline and EOT visits)	
End point type	Primary
End point timeframe:	
Baseline to end of treatment (16 weeks)	

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: 1				
Yes	103	25	26	4
No	102	21	27	18

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: 1				
Yes	6	8		
No	28	22		

Statistical analyses

Statistical analysis title	Combined Logistic regression model Placebo-NTX 12
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Statistical analysis description:

A logistic regression model was used, with treatment (NTX 30 mg/ml, NTX 12 mg/ml, and placebo), the stratification factors at randomisation (EtG of less than 500 ng/ml [abstinent] and nicotine use in the prior week), and the baseline value of WHO Drinking Risk Level as a predictor in the model. The results are presented using model-based estimates of the odd ratios of each active treatment group versus the placebo group with corresponding 95% confidence intervals (CIs) and P values.

Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9204 ^[1]
Method	Regression, Logistic

Notes:

[1] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined Logistic regression model Placebo-NTX 30
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Statistical analysis description:

A logistic regression model was used, with treatment (NTX 30 mg/ml, NTX 12 mg/ml, and placebo), the stratification factors at randomisation (EtG of less than 500 ng/ml [abstinent] and nicotine use in the prior week), and the baseline value of WHO Drinking Risk Level as a predictor in the model. The results are presented using model-based estimates of the odd ratios of each active treatment group versus the placebo group with corresponding 95% confidence intervals (CIs) and P values.

Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
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Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9289
Method	Regression, Logistic

Secondary: Time to a 2-level risk reduction

End point title	Time to a 2-level risk reduction
End point description:	Time to a 2-level risk reduction in WHO Drinking Risk Level that is maintained until the EOT
End point type	Secondary
End point timeframe:	Baseline until end of treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	206	47	30	
Units: day				
median (full range (min-max))	57 (1 to 92)	57 (1 to 61)	57 (10 to 65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with No Heavy Drinking Days

End point title	Subjects with No Heavy Drinking Days
End point description:	Proportion of subjects with No Heavy Drinking days, by month
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: 1				
Yes	51	17	12	4
No	154	29	41	18

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: 1				
Yes	7	3		
No	27	27		

Statistical analyses

Statistical analysis title	Combined Logistic regression model Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4108 ^[2]
Method	Regression, Linear

Notes:

[2] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined Logistic regression model Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1763 ^[3]
Method	Regression, Linear

Notes:

[3] - Combined p-value for Stage I and Stage II

Secondary: Heavy Drinking Days per Month

End point title	Heavy Drinking Days per Month
End point description:	Percentage heavy drinking days, by month
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: day				
least squares mean (confidence interval 95%)	9.75 (8.50 to 10.99)	7.15 (4.48 to 9.81)	9.02 (6.64 to 11.39)	13.61 (10.77 to 16.46)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: day				
least squares mean (confidence interval 95%)	11.68 (9.57 to 13.79)	11.21 (8.82 to 13.59)		

Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0508 ^[4]
Method	ANCOVA

Notes:

[4] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153 ^[5]
Method	ANCOVA

Notes:

[5] - Combined p-value for Stage I and Stage II

Secondary: Consecutive Days of Abstinence

End point title	Consecutive Days of Abstinence
End point description:	
Number of consecutive days abstinent during treatment, by month	
End point type	Secondary

End point timeframe:
Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: day				
least squares mean (confidence interval 95%)	4.54 (3.61 to 5.46)	5.11 (3.10 to 7.12)	4.50 (2.72 to 6.27)	3.12 (1.03 to 5.21)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: day				
least squares mean (confidence interval 95%)	3.41 (1.79 to 5.03)	2.62 (0.88 to 4.35)		

Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486 ^[6]
Method	ANCOVA

Notes:

[6] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9737 ^[7]
Method	ANCOVA

Notes:

[7] - Combined p-value for Stage I and Stage II

Secondary: Mean Total Alcohol Grams per Day

End point title	Mean Total Alcohol Grams per Day
End point description:	Mean total alcohol grams per day, by month
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: alcohol grams per day				
least squares mean (confidence interval 95%)	52.99 (47.78 to 58.20)	44.65 (33.82 to 55.47)	45.64 (35.64 to 55.64)	62.53 (53.03 to 72.04)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: alcohol grams per day				
least squares mean (confidence interval 95%)	58.47 (51.21 to 65.73)	56.82 (48.85 to 64.78)		

Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2083 [8]
Method	ANCOVA

Notes:

[8] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0463 [9]
Method	ANCOVA

Notes:

[9] - Combined p-value for Stage I and Stage II

Secondary: Drinking Days per Month

End point title	Drinking Days per Month
End point description:	Percentage of drinking days, by month
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: day				
least squares mean (confidence interval 95%)	19.00 (17.89 to 20.12)	17.18 (14.82 to 19.54)	17.48 (15.33 to 19.62)	21.68 (19.33 to 24.03)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: day				
least squares mean (confidence interval 95%)	20.66 (18.91 to 22.40)	22.57 (20.63 to 24.52)		

Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Naltrexone 12 v Placebo

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.255 ^[10]
Method	ANCOVA

Notes:

[10] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4184 ^[11]
Method	ANCOVA

Notes:

[11] - Combined p-value for Stage I and Stage II

Secondary: 1-level reduction in WHO Drinking Risk Level

End point title	1-level reduction in WHO Drinking Risk Level
End point description:	The proportion of subjects showing an improvement in WHO Drinking Risk Level consisting of a 1-level reduction from Baseline to EOT
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205	46	53	22
Units: 1				
Yes	150	37	42	7
No	55	9	11	15

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: 1				
Yes	22	20		
No	12	10		

Statistical analyses

Statistical analysis title	Combined Logistic regression model Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0169 ^[12]
Method	Regression, Logistic

Notes:

[12] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined Logistic regression model Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0338 ^[13]
Method	Regression, Logistic

Notes:

[13] - Combined p-value for Stage I and Stage II

Secondary: Alcohol Craving

End point title	Alcohol Craving
End point description:	Alcohol craving by month (Mini Alcohol Craving Experience Questionnaire)
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	187	41	46	8
Units: MACE score				
least squares mean (confidence interval 95%)	15.88 (14.40 to 17.35)	12.56 (9.41 to 15.71)	16.57 (13.67 to 19.48)	9.49 (4.83 to 14.15)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	20		
Units: MACE score				
least squares mean (confidence interval 95%)	9.97 (5.73 to 14.22)	11.56 (8.40 to 14.72)		

Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0339 ^[14]
Method	ANCOVA

Notes:

[14] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8769 ^[15]
Method	ANCOVA

Notes:

[15] - Combined p-value for Stage I and Stage II

Secondary: Nicotine use

End point title	Nicotine use
End point description:	Change in nicotine use from Baseline to Week 16
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	23	20	9
Units: mg				
arithmetic mean (standard deviation)	-6 (± 24.06)	-7.1 (± 40.99)	-1.5 (± 12.44)	1.1 (± 3.38)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: mg				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Positive and Negative Affect Scale

End point title	Positive and Negative Affect Scale
End point description:	Positive Affect scores by month
End point type	Secondary
End point timeframe:	Baseline to End of Treatment

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	187	41	46	8
Units: PANAS score				
least squares mean (confidence interval 95%)	28.01 (27.04 to 28.98)	29.27 (27.12 to 31.42)	27.65 (25.70 to 29.53)	23.47 (18.90 to 28.04)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	20		
Units: PANAS score				
least squares mean (confidence interval)	28.03 (24.20)	27.38 (24.15)		

95%)	to 31.85)	to 30.61)
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Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.087 ^[16]
Method	ANCOVA

Notes:

[16] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6596 ^[17]
Method	ANCOVA

Notes:

[17] - Combined p-value for Stage I and Stage II

Secondary: Positive and Negative Affect Scale

End point title	Positive and Negative Affect Scale
End point description:	
Negative Affect score	
End point type	Secondary
End point timeframe:	
Baseline to End of Treatment	

End point values	Placebo	Naltrexone 12	Naltrexone 30	Placebo Non-responder Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	187	41	46	8
Units: PANAS score				
least squares mean (confidence interval 95%)	17.82 (16.93 to 18.71)	17.07 (15.19 to 18.96)	18.58 (16.82 to 20.33)	18.28 (13.65 to 22.91)

End point values	Placebo Non-responder Naltrexone 12	Placebo Non-responder Naltrexone 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	20		
Units: PANAS score				
least squares mean (confidence interval 95%)	13.91 (9.71 to 18.10)	15.06 (11.88 to 18.23)		

Statistical analyses

Statistical analysis title	Combined ANCOVA Placebo-NTX 12
Comparison groups	Placebo Non-responder Naltrexone 12 v Placebo v Naltrexone 12 v Placebo Non-responder Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1196 ^[18]
Method	ANCOVA

Notes:

[18] - Combined p-value for Stage I and Stage II

Statistical analysis title	Combined ANCOVA Placebo-NTX 30
Comparison groups	Placebo Non-responder Placebo v Placebo Non-responder Naltrexone 30 v Placebo v Naltrexone 30
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5893 ^[19]
Method	ANCOVA

Notes:

[19] - Combined p-value for Stage I and Stage II

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 Jan 2022 - 14 Feb 2023

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Placebo + Placebo - Stage I
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Reporting group description: -

Reporting group title	Placebo + Placebo - Stage II
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Reporting group description: -

Reporting group title	Placebo + NTX 12 - Stage I
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Reporting group description: -

Reporting group title	Placebo + NTX 12 - Stage II
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Reporting group description: -

Reporting group title	Placebo + NTX 30 - Stage I
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Reporting group description: -

Reporting group title	Placebo + NTX 30 - Stage II
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Reporting group description: -

Reporting group title	NTX 12 + NTX 12 - Stage I
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Reporting group description: -

Reporting group title	NTX 12 + NTX 12 - Stage II
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Reporting group description: -

Reporting group title	NTX 30 + NTX 30 - Stage I
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Reporting group description: -

Reporting group title	NTX 30 + NTX 30 - Stage II
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Reporting group description: -

Serious adverse events	Placebo + Placebo - Stage I	Placebo + Placebo - Stage II	Placebo + NTX 12 - Stage I
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 142 (0.70%)	2 / 123 (1.63%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Limb traumatic amputation			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Fatal accident			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Binge drinking			
subjects affected / exposed	1 / 142 (0.70%)	1 / 123 (0.81%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Behaviour disorder due to a general medical condition			
subjects affected / exposed	0 / 142 (0.00%)	1 / 123 (0.81%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder due to a general medical condition			
subjects affected / exposed	0 / 142 (0.00%)	1 / 123 (0.81%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + NTX 12 - Stage II	Placebo + NTX 30 - Stage I	Placebo + NTX 30 - Stage II
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	1 / 30 (3.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Limb traumatic amputation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatal accident			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Binge drinking			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Behaviour disorder due to a general medical condition			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder due to a general medical condition			

subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	NTX 12 + NTX 12 - Stage I	NTX 12 + NTX 12 - Stage II	NTX 30 + NTX 30 - Stage I
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	0 / 53 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Injury, poisoning and procedural complications			
Limb traumatic amputation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatal accident			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Rash erythematous subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Binge drinking subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Behaviour disorder due to a general medical condition			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder due to a general medical condition			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	NTX 30 + NTX 30 - Stage II		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 46 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Limb traumatic amputation			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatal accident			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Binge drinking			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Behaviour disorder due to a general medical condition			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental disorder due to a general medical condition			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	Placebo + Placebo - Stage I	Placebo + Placebo - Stage II	Placebo + NTX 12 - Stage I
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 142 (40.14%)	28 / 123 (22.76%)	12 / 34 (35.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 142 (2.82%)	2 / 123 (1.63%)	0 / 34 (0.00%)
occurrences (all)	4	3	0
Surgical and medical procedures			
Bone graft			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Dental prosthesis placement			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 142 (2.11%)	0 / 123 (0.00%)	1 / 34 (2.94%)
occurrences (all)	5	0	2
Asthenia			

subjects affected / exposed	4 / 142 (2.82%)	1 / 123 (0.81%)	0 / 34 (0.00%)
occurrences (all)	5	1	0
Chills			
subjects affected / exposed	1 / 142 (0.70%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	12 / 142 (8.45%)	2 / 123 (1.63%)	4 / 34 (11.76%)
occurrences (all)	16	2	4
Nasal discomfort			
subjects affected / exposed	12 / 142 (8.45%)	2 / 123 (1.63%)	2 / 34 (5.88%)
occurrences (all)	21	3	3
Nasal inflammation			
subjects affected / exposed	3 / 142 (2.11%)	1 / 123 (0.81%)	2 / 34 (5.88%)
occurrences (all)	4	1	2
Sneezing			
subjects affected / exposed	5 / 142 (3.52%)	3 / 123 (2.44%)	1 / 34 (2.94%)
occurrences (all)	11	6	1
Epistaxis			
subjects affected / exposed	2 / 142 (1.41%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Nasal congestion			
subjects affected / exposed	2 / 142 (1.41%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Rhinalgia			

subjects affected / exposed	1 / 142 (0.70%)	1 / 123 (0.81%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 142 (0.70%)	2 / 123 (1.63%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	3 / 142 (2.11%)	3 / 123 (2.44%)	0 / 34 (0.00%)
occurrences (all)	3	4	0
Nasal pruritus			
subjects affected / exposed	3 / 142 (2.11%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
Throat irritation			
subjects affected / exposed	3 / 142 (2.11%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	4	0	0
Intranasal paraesthesia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Hyperactive pharyngeal reflex			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 142 (7.04%)	1 / 123 (0.81%)	2 / 34 (5.88%)
occurrences (all)	13	1	2
Sleep disorder			
subjects affected / exposed	3 / 142 (2.11%)	2 / 123 (1.63%)	0 / 34 (0.00%)
occurrences (all)	3	2	0
Anxiety			
subjects affected / exposed	2 / 142 (1.41%)	1 / 123 (0.81%)	0 / 34 (0.00%)
occurrences (all)	4	5	0
Claustrophobia			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Depersonalisation/derealisation disorder			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	2 / 142 (1.41%)	1 / 123 (0.81%)	1 / 34 (2.94%)
occurrences (all)	3	1	1
Product issues			
Product taste abnormal			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 142 (0.70%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 142 (14.08%)	6 / 123 (4.88%)	5 / 34 (14.71%)
occurrences (all)	45	12	6
Dizziness			
subjects affected / exposed	4 / 142 (2.82%)	2 / 123 (1.63%)	0 / 34 (0.00%)
occurrences (all)	5	2	0
Somnolence			
subjects affected / exposed	5 / 142 (3.52%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	6	0	0
Neuralgia			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 142 (0.00%)	0 / 123 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Lacrimation increased subjects affected / exposed occurrences (all)	2 / 142 (1.41%) 3	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Eye pruritus subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	1 / 34 (2.94%) 1
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	4 / 142 (2.82%) 6	0 / 123 (0.00%) 0	1 / 34 (2.94%) 1
Abdominal pain subjects affected / exposed occurrences (all)	1 / 142 (0.70%) 1	0 / 123 (0.00%) 0	2 / 34 (5.88%) 4
Diarrhoea subjects affected / exposed occurrences (all)	3 / 142 (2.11%) 5	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	5 / 142 (3.52%) 8	1 / 123 (0.81%) 2	0 / 34 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Crohn's disease subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 142 (1.41%) 2	1 / 123 (0.81%) 1	0 / 34 (0.00%) 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 142 (0.70%) 1	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Eczema			

subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed occurrences (all)	3 / 142 (2.11%) 3	1 / 123 (0.81%) 1	1 / 34 (2.94%) 1
Pharyngitis			
subjects affected / exposed occurrences (all)	1 / 142 (0.70%) 1	1 / 123 (0.81%) 2	0 / 34 (0.00%) 0
Upper respiratory tract infection			
subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Rhinitis			
subjects affected / exposed occurrences (all)	1 / 142 (0.70%) 1	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
COVID-19			
subjects affected / exposed occurrences (all)	3 / 142 (2.11%) 3	1 / 123 (0.81%) 1	0 / 34 (0.00%) 0
Conjunctivitis			
subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	1 / 123 (0.81%) 1	0 / 34 (0.00%) 0
Sinusitis			
subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Varicella			
subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	1 / 142 (0.70%) 2	1 / 123 (0.81%) 1	0 / 34 (0.00%) 0
Increased appetite			
subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Gout			

subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	0 / 34 (0.00%) 0
Alcohol intolerance subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	0 / 123 (0.00%) 0	1 / 34 (2.94%) 1

Non-serious adverse events	Placebo + NTX 12 - Stage II	Placebo + NTX 30 - Stage I	Placebo + NTX 30 - Stage II
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 34 (26.47%)	13 / 30 (43.33%)	9 / 30 (30.00%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Surgical and medical procedures Bone graft subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Dental prosthesis placement subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Asthenia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 30 (6.67%) 2	1 / 30 (3.33%) 1
Chills subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Injection site pain subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0

Pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 34 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Nasal discomfort			
subjects affected / exposed	0 / 34 (0.00%)	4 / 30 (13.33%)	4 / 30 (13.33%)
occurrences (all)	0	15	4
Nasal inflammation			
subjects affected / exposed	1 / 34 (2.94%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	2	3	2
Sneezing			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 34 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	7	0
Rhinalgia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Cough			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nasal pruritus			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Throat irritation			

subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Intranasal paraesthesia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Hyperactive pharyngeal reflex subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Claustrophobia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Depersonalisation/derealisation disorder subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Alcohol withdrawal syndrome subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Depressed mood subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Product issues			

Product taste abnormal subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	3 / 30 (10.00%) 3
Injury, poisoning and procedural complications Joint injury subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	4 / 30 (13.33%) 7	1 / 30 (3.33%) 1
Dizziness subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 2	0 / 30 (0.00%) 0
Neuralgia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Ear and labyrinth disorders Ear congestion subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 3	0 / 30 (0.00%) 0
Eye pruritus subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	2 / 30 (6.67%) 3
Abdominal pain			

subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1
Toothache subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Crohn's disease subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Eczema subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Rhinitis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
COVID-19 subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 2	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Varicella subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Increased appetite subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Alcohol intolerance subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0

Non-serious adverse events	NTX 12 + NTX 12 - Stage I	NTX 12 + NTX 12 - Stage II	NTX 30 + NTX 30 - Stage I
Total subjects affected by non-serious adverse events subjects affected / exposed	23 / 47 (48.94%)	9 / 41 (21.95%)	28 / 53 (52.83%)
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	0 / 41 (0.00%) 0	1 / 53 (1.89%) 1
Surgical and medical procedures Bone graft subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Dental prosthesis placement subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 6	0 / 41 (0.00%) 0	1 / 53 (1.89%) 1
Asthenia subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Chills subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Injection site pain subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	1 / 41 (2.44%) 1	10 / 53 (18.87%) 16
Nasal discomfort subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 6	0 / 41 (0.00%) 0	5 / 53 (9.43%) 7

Nasal inflammation			
subjects affected / exposed	5 / 47 (10.64%)	0 / 41 (0.00%)	1 / 53 (1.89%)
occurrences (all)	6	0	1
Sneezing			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	3 / 53 (5.66%)
occurrences (all)	1	0	4
Epistaxis			
subjects affected / exposed	3 / 47 (6.38%)	0 / 41 (0.00%)	2 / 53 (3.77%)
occurrences (all)	3	0	2
Nasal congestion			
subjects affected / exposed	1 / 47 (2.13%)	1 / 41 (2.44%)	2 / 53 (3.77%)
occurrences (all)	1	1	4
Rhinalgia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	3 / 53 (5.66%)
occurrences (all)	1	0	4
Oropharyngeal pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2
Nasal pruritus			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Throat irritation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Intranasal paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Hyperactive pharyngeal reflex			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0

Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	3
Sleep disorder			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	3
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Claustrophobia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Depersonalisation/derealisation disorder			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	1 / 47 (2.13%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Product issues			
Product taste abnormal			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 41 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 47 (12.77%)	2 / 41 (4.88%)	10 / 53 (18.87%)
occurrences (all)	6	2	16
Dizziness			

subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 8	1 / 41 (2.44%) 1	3 / 53 (5.66%) 8
Somnolence subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	0 / 41 (0.00%) 0	3 / 53 (5.66%) 6
Neuralgia subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Ear and labyrinth disorders Ear congestion subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	0 / 41 (0.00%) 0	2 / 53 (3.77%) 3
Eye pruritus subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	2 / 41 (4.88%) 2	3 / 53 (5.66%) 5
Abdominal pain subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	1 / 53 (1.89%) 3
Diarrhoea subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	2 / 53 (3.77%) 2
Toothache subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 41 (2.44%) 1	1 / 53 (1.89%) 2
Dry mouth subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	1 / 53 (1.89%) 1
Paraesthesia oral			

subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Crohn's disease subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	1 / 53 (1.89%) 1
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 2	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	0 / 41 (0.00%) 0	3 / 53 (5.66%) 3
Pharyngitis subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	1 / 41 (2.44%) 1	0 / 53 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	1 / 53 (1.89%) 1
COVID-19 subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Sinusitis			

subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Varicella subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0
Increased appetite subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	2 / 53 (3.77%) 2
Gout subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	1 / 53 (1.89%) 1
Alcohol intolerance subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 41 (0.00%) 0	0 / 53 (0.00%) 0

Non-serious adverse events	NTX 30 + NTX 30 - Stage II		
Total subjects affected by non-serious adverse events subjects affected / exposed	14 / 46 (30.43%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Surgical and medical procedures Bone graft subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Dental prosthesis placement subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
General disorders and administration site conditions Fatigue			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Nasal discomfort			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Nasal inflammation			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	2		
Nasal congestion			

subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Rhinalgia subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Cough subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Nasal pruritus subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Throat irritation subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Intranasal paraesthesia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Hyperactive pharyngeal reflex subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Sleep disorder subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Anxiety subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		

Claustrophobia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Depersonalisation/derealisation disorder subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Alcohol withdrawal syndrome subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Depressed mood subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Product issues Product taste abnormal subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Injury, poisoning and procedural complications Joint injury subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Dizziness subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Somnolence subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Neuralgia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Ear and labyrinth disorders Ear congestion			

subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Eye pruritus subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2		
Abdominal pain subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Toothache subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Dry mouth subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Crohn's disease subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Skin and subcutaneous tissue disorders			

Hyperhidrosis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Increased appetite			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Gout			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Alcohol intolerance			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2020	<ul style="list-style-type: none">• Clarified thresholds for Screening liver function test levels• Clarified thresholds for breath alcohol test results
15 June 2022	<ul style="list-style-type: none">• Clarified the WHO Drinking Risk level of High Risk or Very High Risk and its calculation from the TLFB interview• Provided that, in exceptional circumstances and following approval from the Sponsor, the IMP could be dispensed at unscheduled and nondispensing visits• Added subject numbering information• Clarified the requirement for a follow-up call after the Early Withdrawal Visit where possible

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Randomisation was not conducted per protocol due to an IWRS set-up error. The designed treatment allocation ratio at both stages could not be achieved. This issue was identified during final analysis and a Notification of Serious Breach was reported.

Notes: