Clinical trial results:
In search for an innovative neural marker and intervention for socio-communicative difficulties in children with and without autism spectrum disorders

Summary

EudraCT number	2018-000769-35
Trial protocol	BE
Global end of trial date	30 August 2021

Results information

Result version number	v1 (current)
This version publication date	18 March 2022
First version publication date	18 March 2022
Summary attachment (see zip file)	MOX study (MOX study – Description.pdf)

Trial information

Trial identification

Sponsor protocol code	S61358

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Hospital Leuven / KU Leuven
Sponsor organisation address	Oude Markt 13, Leuven, Belgium, 3000
Public contact	Prof. Dr. K. Alaerts, University Hospital, KU Leuven, 0032 16376446, kaat.alaerts@kuleuven.be
Scientific contact	Prof. Dr. K. Alaerts, University Hospital, KU Leuven, 0032 16376446, kaat.alaerts@kuleuven.be

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	30 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2021
Global end of trial reached?	Yes
Global end of trial date	30 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Exploring the effects and mechanism of multiple-dose oxytocin treatment (OT) in children with Autism Spectrum Disorders (ASD) (age 8-12 years).

The principal aim of the current clinical trial is to explore the effects and mechanism of multiple-dose OT treatment in children with ASD, by assessing the effects of treatment both at the neural and the behavioral level.

Protection of trial subjects:

Regular screenings of potential side-effects

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	69
Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Children with ASD were recruited mainly via the Expertise Centrum Autisme (ECA) of the UZ Leuven between July 2019 and January 2021.

Pre-assignment

Screening details:

Screening details:

Assessed for eligibility (n= 101)
Included: 80
Excluded: 21
not meeting inclusion criteria n = 5
declined to participate n = 16
other reasons n = 0

Period 1

Period 1 title	Phase 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

In phase I, half of the patients will receive oxytocin nasal sprays while the other half will receive placebo nasal sprays. All patients, their parents, and investigators involved in the data collection and analysis will be blind with respect to the allocated treatment condition.

Arms

Are arms mutually exclusive?	Yes
Arm title	Oxytocin

Arm description:

OT (Syntocinon®) was administered using a twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. They had to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Arm type	Experimental
Investigational medicinal product name	Syntocinon® nasal spray (40 IU/ml)
Investigational medicinal product code	RVG 03716
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. The participants will be asked to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Arm title	Placebo

Arm description:

Physiological water, sodium chloride (NaCl .9%) solution, with added preservatives (aqua conservans, chlorbutanol, glycerin) was used for the placebo (PL) nasal spray. Participants had to administer the spray daily in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril).

Arm type	Placebo

Investigational medicinal product name	Placebo (Physiological water, sodium chloride (NaCl .9%) solution, with added preservatives (aqua conservans, chlorbutanol, glycerin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Physiological water, sodium chloride (NaCl .9%) solution, with added preservatives (aqua conservans, chlorbutanol, glycerin) was used for the placebo (PL) nasal spray.
They had to administer the spray daily in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff) during four weeks.

Number of subjects in period 1	Oxytocin	Placebo
Started	40	40
Completed	40	40

Period 2

Period 2 title	Phase II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Both groups of phase I (OT and placebo) received the real multiple-dose OT intervention. Hence, the investigators conducting the trial were no longer blind with respect to the received treatment (all OT). The parents of the participating children were informed that all children will receive the real OT treatment during at least one of the two administration months. All patients and their parents were blind to the treatment assignment, since the order of the treatment phases was concealed.

Arms

Are arms mutually exclusive?	Yes
Arm title	OT - first

Arm description:

Administration via nasal spray Syntocinon® (Oxytocin): Syntocinon nasal spray. A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU during four weeks. They had to administer the spray in the morning and in the afternoon by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Arm type	Experimental
Investigational medicinal product name	Syntocinon® nasal spray (40 IU/ml)
Investigational medicinal product code	RVG 03716
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. The participants will be asked to

administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Arm title	PL - first

Arm description:

Administration via nasal spray Syntocinon® (Oxytocin): Syntocinon nasal spray. A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU during four weeks. They had to administer the spray in the morning and in the afternoon by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Arm type	Experimental
Investigational medicinal product name	Syntocinon® nasal spray (40 IU/ml)
Investigational medicinal product code	RVG 03716
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. The participants will be asked to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Number of subjects in period 2[1]	OT - first	PL - first
Started	38	39
Completed	38	39

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of subjects starting the period Phase II is not consistent with the number completing the preceding period because 3 subjects (Oxytocin n = 2, Placebo n = 1) withdrew their consent to participate due to time constraints.

Baseline characteristics

Reporting groups	
Reporting group title	Oxytocin
Reporting group description:	
OT (Syntocinon®) was administered using a twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. They had to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).	
Reporting group title	Placebo
Reporting group description:	
Physiological water, sodium chloride (NaCl .9%) solution, with added preservatives (aqua conservans, chlorbutanol, glycerin) was used for the placebo (PL) nasal spray. Participants had to administer the spray daily in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril).	

Reporting group values	Oxytocin	Placebo	Total
Number of subjects	40	40	80
Age categorical Units: Subjects			
Children (2-11 years)	34	35	69
Adolescents (12-17 years)	6	5	11
Age continuous Units: years			
arithmetic mean	10.53	10.45	
standard deviation	± 1.35	± 1.27	-
Gender categorical Units: Subjects			
Female	8	8	16
Male	32	32	64
Total IQ Units: units on a scale			
arithmetic mean	104.03	105.60	
standard deviation	± 13.10	± 11.38	-

End points

End points reporting groups

Reporting group title	Oxytocin
Reporting group description:	
OT (Syntocinon®) was administered using a twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. They had to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).	
Reporting group title	Placebo
Reporting group description:	
Physiological water, sodium chloride (NaCl .9%) solution, with added preservatives (aqua conservans, chlorbutanol, glycerin) was used for the placebo (PL) nasal spray. Participants had to administer the spray daily in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril).	
Reporting group title	OT - first
Reporting group description:	
Administration via nasal spray Syntocinon® (Oxytocin): Syntocinon nasal spray. A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU during four weeks. They had to administer the spray in the morning and in the afternoon by administering six puffs (three puffs in each nosetril; 2 IU/ puff).	
Reporting group title	PL - first
Reporting group description:	
Administration via nasal spray Syntocinon® (Oxytocin): Syntocinon nasal spray. A twice daily intranasal dose of 12 IU resulting a daily dose of 24IU during four weeks. They had to administer the spray in the morning and in the afternoon by administering six puffs (three puffs in each nosetril; 2 IU/ puff).	
Subject analysis set title	Phase 1 Post OT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 1 T1 - OT	
Subject analysis set title	Phase 1 Follow-up OT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 1 T2 OT	
Subject analysis set title	Phase 1 Post PL
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 1 T1 PL	
Subject analysis set title	Phase 1 Follow-up PL
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 1 T2 PL	
Subject analysis set title	Phase 2 Post OT First
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 2 Post T3 OT	
Subject analysis set title	Phase 2 Follow-up OT First
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 2 T4 OT	
Subject analysis set title	Phase 2 Post PL First
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Phase 2 T3 (PL First)	
Subject analysis set title	Phase 2 Follow-up PL First

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Phase 2 T4 (PL First)

Primary: Change from baseline in caregiver-rated scores on questionnaire assessing social functioning after 4 weeks of nasal spray

End point title	Change from baseline in caregiver-rated scores on questionnaire assessing social functioning after 4 weeks of nasal spray

End point description:

Social responsiveness Scale-Children (SRS) - caregiver-rated - four-point Likert-scale - higher scores indicate lower social responsiveness

End point type	Primary

End point timeframe:

Value at 4 weeks minus value at baseline

End point values	Phase 1 Post OT	Phase 1 Post PL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)	-4.08 (± 10.05)	-4.55 (± 10.23)		

Statistical analyses

Statistical analysis title	SRS after 4 weeks of nasal spray

Statistical analysis description:

Between-group differences in treatment responses of phase I (double-blind) were assessed, by subjecting change from baseline scores of the post session to independent sample t-tests.

Comparison groups	Phase 1 Post OT v Phase 1 Post PL
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.839
Method	t-test, 2-sided

Primary: Change from baseline in caregiver-rated scores on questionnaire assessing social functioning after 8 weeks, including 4 weeks without nasal spray

End point title	Change from baseline in caregiver-rated scores on questionnaire assessing social functioning after 8 weeks, including 4 weeks without nasal spray

End point description:

Social responsiveness Scale-Children (SRS) - caregiver-rated - four-point Likert-scale - higher scores indicate lower social responsiveness

End point type	Primary

End point timeframe:

Value at 8 weeks minus value at baseline

End point values	Phase 1 Follow-up OT	Phase 1 Follow-up PL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	39		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)	-6.76 (± 11.19)	-5.38 (± 13.42)		

Statistical analyses

Statistical analysis title	SRS after 8 weeks, including 4 weeks without nasal

Statistical analysis description:

Between-group differences in treatment responses of phase I (double-blind) were assessed, by subjecting change from baseline scores of the follow-up session to independent sample t-tests.

Comparison groups	Phase 1 Follow-up OT v Phase 1 Follow-up PL
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.626
Method	t-test, 2-sided

Secondary: Change from baseline in caregiver-rated scores on questionnaire assessing repetitive behaviors and anxiety after 4 weeks of nasal spray

End point title	Change from baseline in caregiver-rated scores on questionnaire assessing repetitive behaviors and anxiety after 4 weeks of nasal spray

End point description:

Repetitive Behavior Scale-Revised (RBS-R) – caregiver-rated – four-point Likert-scale – higher scores indicate more severe repetitive behavior
Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – caregiver-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder

End point type	Secondary

End point timeframe:

Value at 4 weeks minus value at baseline

End point values	Phase 1 Post OT	Phase 1 Post PL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
RBS	-6.53 (± 11.26)	-6.76 (± 9.92)		
SCARED caregiver report	-0.47 (± 11.61)	-4.95 (± 11.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in self-report scores on questionnaire assessing attachment and anxiety after 4 weeks of nasal spray

End point title	Change from baseline in self-report scores on questionnaire assessing attachment and anxiety after 4 weeks of nasal spray

End point description:

Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – self-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder
Attachment Style Classification Questionnaire (ASQ), three scales: secure, anxious or avoidant – self-report – five-point Likert-scale – higher scores indicate a more secure, anxious or avoidant attachment toward their peers
Attachment questionnaire, three scales: trust, anxiety and avoidance – self-report – seven-point Likert-scale – higher scores indicate more trust, anxiety or avoidance towards their mother

End point type	Secondary

End point timeframe:

Value at 4 weeks minus value at baseline

End point values	Phase 1 Post OT	Phase 1 Post PL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	39		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
SCARED self report	-4.74 (± 11.47)	-3.38 (± 11.32)		
ASQ - secure	-0.89 (± 2.42)	-0.92 (± 2.93)		
ASQ - anxious	-0.92 (± 3.24)	-1.00 (± 2.50)		
ASQ - avoidant	-0.29 (± 3.73)	-1.08 (± 3.30)		
Attachment peers - anxiety	0.76 (± 2.95)	-0.33 (± 2.57)		
Attachment peers - avoidance	-0.21 (± 3.18)	-0.82 (± 3.94)		
Attachment peers - trust	0.24 (± 4.18)	-0.18 (± 2.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in caregiver-rated scores on questionnaire assessing repetitive behaviors and anxiety after 8 weeks, including 4 weeks without nasal spray

End point title	Change from baseline in caregiver-rated scores on questionnaire assessing repetitive behaviors and anxiety after 8 weeks, including 4 weeks without nasal spray

End point description:

Repetitive Behavior Scale-Revised (RBS-R) – caregiver-rated – four-point Likert-scale – higher scores indicate more severe repetitive behavior
Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – caregiver-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder

End point type	Secondary

End point timeframe:

Value at 8 weeks minus value at baseline

End point values	Phase 1 Follow-up OT	Phase 1 Follow-up PL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	39		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
RBS	-4.55 (± 10.76)	-4.41 (± 8.28)		
SCARED caregiver rated	-2.92 (± 11.53)	-5.38 (± 9.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in self-report scores on questionnaire assessing attachment and anxiety after 8 weeks, including 4 weeks without nasal spray

End point title	Change from baseline in self-report scores on questionnaire assessing attachment and anxiety after 8 weeks, including 4 weeks without nasal spray

End point description:

Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – self-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder
Attachment Style Classification Questionnaire (ASQ), three scales: secure, anxious or avoidant – self-report – five-point Likert-scale – higher scores indicate a more secure, anxious or avoidant attachment toward their peers.
Attachment questionnaire, three scales: trust, anxiety and avoidance – self-report – seven-point Likert-scale – higher scores indicate more trust, anxiety or avoidance towards their mother.

End point type	Secondary

End point timeframe:

Value at 8 weeks minus value at baseline

End point values	Phase 1 Follow-up OT	Phase 1 Follow-up PL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	39		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
SCARED self report	-5.97 (± 9.84)	-6.36 (± 13.38)		
ASQ - secure	-1.37 (± 3.34)	-0.82 (± 3.78)		
ASQ - anxious	-1.00 (± 3.92)	-2.38 (± 3.75)		
ASQ - avoidant	-0.84 (± 4.04)	-1.46 (± 3.09)		
Attachment peers - anxiety	0.84 (± 3.11)	0.08 (± 3.07)		
Attachment peers - avoidance	-0.61 (± 3.89)	-0.67 (± 3.50)		
Attachment peers - trust	0.66 (± 3.93)	0.13 (± 2.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in caregiver-rated scores on questionnaires assessing social functioning, repetitive behaviors and anxiety after 12 weeks, including 8 weeks of intermittent nasal spray

End point title	Change from baseline in caregiver-rated scores on questionnaires assessing social functioning, repetitive behaviors and anxiety after 12 weeks, including 8 weeks of intermittent nasal spray

End point description:

Social responsiveness Scale-Children (SRS) - caregiver-rated - four-point Likert-scale - higher scores indicate lower social responsiveness
Repetitive Behavior Scale-Revised (RBS-R) – caregiver-rated – four-point Likert-scale – higher scores indicate more severe repetitive behavior
Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – caregiver-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder

End point type	Secondary

End point timeframe:

Value at 12 weeks minus value at baseline

End point values	Phase 2 Post OT First	Phase 2 Post PL First		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
SRS	-5.57 (± 13.24)	-10.84 (± 14.77)		
RBS	-6.46 (± 11.96)	-7.13 (± 8.54)		
SCARED caregiver report	-2.95 (± 9.80)	-7.18 (± 10.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in self-report scores on questionnaires assessing attachment and anxiety after 12 weeks, including 8 weeks of intermittent nasal spray

End point title	Change from baseline in self-report scores on questionnaires assessing attachment and anxiety after 12 weeks, including 8 weeks of intermittent nasal spray

End point description:

Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – self-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder
Attachment questionnaire, three scales: trust, anxiety and avoidance – self-report – seven-point Likert-scale – higher scores indicate more trust, anxiety or avoidance towards their mother
Attachment Style Classification Questionnaire (ASQ), three scales: secure, anxious or avoidant – self-report – five-point Likert-scale – higher scores indicate a more secure, anxious or avoidant attachment toward their peers

End point type	Secondary

End point timeframe:

Value at 12 weeks minus value at baseline

End point values	Phase 2 Post OT First	Phase 2 Post PL First		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
SCARED self report	-8.65 (± 14.26)	-7.23 (± 16.85)		
ASQ - secure	-1.51 (± 3.68)	-0.82 (± 3.60)		
ASQ - anxious	-1.32 (± 5.03)	-2.44 (± 3.78)		

ASQ - avoidant	-1.51 (± 4.27)	-1.31 (± 3.33)		
Attachment peers - anxiety	0.92 (± 3.77)	0.31 (± 3.46)		
Attachment peers - avoidance	-0.84 (± 4.17)	-1.13 (± 3.47)		
Attachment peers - trust	0.32 (± 4.77)	-0.85 (± 3.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in caregiver-rated scores on questionnaires assessing social functioning, repetitive behaviors and anxiety after 16 weeks, including 8 weeks of intermittent nasal spray

End point title	Change from baseline in caregiver-rated scores on questionnaires assessing social functioning, repetitive behaviors and anxiety after 16 weeks, including 8 weeks of intermittent nasal spray

End point description:

Social responsiveness Scale-Children (SRS) – caregiver-rated – four-point Likert-scale – higher scores indicate lower social responsiveness
Repetitive Behavior Scale-Revised (RBS-R) – caregiver-rated – four-point Likert-scale – higher scores indicate more severe repetitive behavior
Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – caregiver-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder

End point type	Secondary

End point timeframe:

Value at 16 weeks minus value at baseline

End point values	Phase 2 Follow-up OT First	Phase 2 Follow-up PL First		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	36		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
SRS	-9.61 (± 12.18)	-9.81 (± 14.83)		
RBS	-7.53 (± 12.88)	-7.83 (± 9.35)		
SCARED caregiver report	-5.72 (± 13.04)	-8.17 (± 10.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in self-report scores on questionnaires assessing attachment and anxiety after 16 weeks, including 8 weeks of intermittent nasal spray

End point title	Change from baseline in self-report scores on questionnaires assessing attachment and anxiety after 16 weeks, including 8 weeks of intermittent nasal spray

End point description:

Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) – self-rated – three-point Likert scale – higher scores indicate greater risk for an anxiety disorder
Attachment questionnaire, three scales: trust, anxiety and avoidance – self-report – seven-point Likert-scale – higher scores indicate more trust, anxiety or avoidance towards their mother
Attachment Style Classification Questionnaire (ASQ), three scales: secure, anxious or avoidant – self-report – five-point Likert-scale – higher scores indicate a more secure, anxious or avoidant attachment toward their peers

End point type	Secondary

End point timeframe:

Value at 16 weeks minus value at baseline

End point values	Phase 2 Follow-up OT First	Phase 2 Follow-up PL First		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: Change from base (units on a scale)				
arithmetic mean (standard deviation)				
SCARED self report	-9.86 (± 17.39)	-10.73 (± 18.14)		
ASQ - secure	-1.72 (± 3.50)	-1.05 (± 3.47)		
ASQ - anxious	-1.44 (± 3.77)	-2.14 (± 4.18)		
ASQ - avoidant	-1.17 (± 3.79)	-0.84 (± 3.85)		
Attachment peers - anxiety	1.00 (± 4.53)	0.11 (± 3.07)		
Attachment peers - avoidance	-0.86 (± 4.00)	-0.73 (± 3.30)		
Attachment peers - trust	0.11 (± 4.37)	-0.38 (± 3.27)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected over a period of (approximately) 4.3 months (131 days). Reporting of AE took place from baseline until end of trial.

Adverse event reporting additional description:

At the end of each week during the course of the daily treatment, parents of the patients were asked to indicate whether or not their child experienced any potential adverse events. A medical person, who is not involved in data analysis or data collection, reviewed all potential adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	Informant-report
Dictionary version	2018

Reporting groups

Reporting group title	Phase 1 - Syntocinon (Oxytocin)

Reporting group description:

Reporting of AE during the first 8 weeks of the trial, administering an OT nasal spray during the first 4 weeks of this reporting time frame
OT (Syntocinon®) was administered using a twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. They had to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Reporting group title	Phase 1 - Placebo (Physiological water(sodium chloride (NaCl)

Reporting group description:

Reporting of AE during the first 8 weeks of the trial, administering an PL nasal spray during the first 4 weeks of this reporting time frame.
Physiological water, sodium chloride (NaCl .9%) solution, with added preservatives (aqua conservans, chlorbutanol, glycerin) was used for the placebo (PL) nasal spray. They had to administer the spray daily in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril) during four weeks.

Reporting group title	Phase 2 - OT first

Reporting group description:

Reporting of AE during the second phase (duration of 8 weeks) of the trial after administering an OT spray in the first phase and administering an OT nasal spray in the first 4 weeks of this second reporting time frame.
OT (Syntocinon®) was administered using a twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. They had to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Reporting group title	Phase 2 - PL first

Reporting group description:

Reporting of AE during the second phase (duration of 8 weeks) of the trial after administering a PL spray in the first phase and administering an OT nasal spray in the first 4 weeks of this second reporting time frame.
OT (Syntocinon®) was administered using a twice daily intranasal dose of 12 IU resulting a daily dose of 24IU. They had to administer the spray in the morning and in the afternoon (right after school) by administering six puffs (three puffs in each nosetril; 2 IU/ puff).

Serious adverse events	Phase 1 - Syntocinon (Oxytocin)	Phase 1 - Placebo (Physiological water(sodium chloride (NaCl)	Phase 2 - OT first
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	4 / 40 (10.00%)	0 / 38 (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			
Fracture			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 38 (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
Social circumstances			
Anger	Additional description: Severe episode of anger, aggression and irritability		
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 38 (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
Infections and infestations			
Viral infection	Additional description: Fever and flu-like symptoms		
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2 - PL first		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Anger	Additional description: Severe episode of anger, aggression and irritability		
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral infection	Additional description: Fever and flu-like symptoms		

subjects affected / exposed	3 / 39 (7.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1 - Syntocinon (Oxytocin)	Phase 1 - Placebo (Physiological water(sodium chloride (NaCl)	Phase 2 - OT first
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 40 (67.50%)	31 / 40 (77.50%)	23 / 38 (60.53%)
Cardiac disorders			
Changes in heart rate or palpitation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	2	0	2
General disorders and administration site conditions			
Headache			
subjects affected / exposed	7 / 40 (17.50%)	7 / 40 (17.50%)	6 / 38 (15.79%)
occurrences (all)	14	9	9
Drowsiness			
subjects affected / exposed	4 / 40 (10.00%)	2 / 40 (5.00%)	2 / 38 (5.26%)
occurrences (all)	8	3	2
Sore throat			
subjects affected / exposed	3 / 40 (7.50%)	5 / 40 (12.50%)	2 / 38 (5.26%)
occurrences (all)	4	8	6
Dry throat/ dry mouth			
subjects affected / exposed	3 / 40 (7.50%)	2 / 40 (5.00%)	3 / 38 (7.89%)
occurrences (all)	3	2	7
Hoarseness			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	3 / 38 (7.89%)
occurrences (all)	1	3	3
Congested nose			
subjects affected / exposed	9 / 40 (22.50%)	7 / 40 (17.50%)	3 / 38 (7.89%)
occurrences (all)	12	11	8
Sneezing			

subjects affected / exposed	6 / 40 (15.00%)	3 / 40 (7.50%)	1 / 38 (2.63%)
occurrences (all)	7	4	1
Nasal irritation			
subjects affected / exposed	5 / 40 (12.50%)	3 / 40 (7.50%)	3 / 38 (7.89%)
occurrences (all)	8	3	6
Runny nose			
subjects affected / exposed	5 / 40 (12.50%)	1 / 40 (2.50%)	2 / 38 (5.26%)
occurrences (all)	6	2	2
Burning sensation in nose and/ or ears			
subjects affected / exposed	4 / 40 (10.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences (all)	7	0	1
Insomnia/ sleep difficulties			
subjects affected / exposed	4 / 40 (10.00%)	4 / 40 (10.00%)	3 / 38 (7.89%)
occurrences (all)	5	4	3
Staring/ daydreams			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	2	0	2
Sensitive for fragrances			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	3
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	6 / 40 (15.00%)	1 / 40 (2.50%)	0 / 38 (0.00%)
occurrences (all)	8	2	0
Eye disorders			
Watery eyes			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	2	0	2
Social circumstances			
Less talk to others			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	1 / 38 (2.63%)
occurrences (all)	2	2	1
Persistent thoughts and/or feelings			
subjects affected / exposed	2 / 40 (5.00%)	5 / 40 (12.50%)	2 / 38 (5.26%)
occurrences (all)	2	7	4
Irritability / anger			

subjects affected / exposed	6 / 40 (15.00%)	7 / 40 (17.50%)	7 / 38 (18.42%)
occurrences (all)	8	11	8
Sad			
subjects affected / exposed	4 / 40 (10.00%)	5 / 40 (12.50%)	4 / 38 (10.53%)
occurrences (all)	4	7	5
Prone to crying or more emotional			
subjects affected / exposed	5 / 40 (12.50%)	9 / 40 (22.50%)	6 / 38 (15.79%)
occurrences (all)	6	15	10
Anxious, worried or discomfort			
subjects affected / exposed	3 / 40 (7.50%)	1 / 40 (2.50%)	4 / 38 (10.53%)
occurrences (all)	5	2	6
Happy or satisfied			
subjects affected / exposed	8 / 40 (20.00%)	14 / 40 (35.00%)	12 / 38 (31.58%)
occurrences (all)	15	27	19
Euphoric or unusually happy			
subjects affected / exposed	5 / 40 (12.50%)	6 / 40 (15.00%)	4 / 38 (10.53%)
occurrences (all)	9	10	6
Calm, relaxed or comfortable			
subjects affected / exposed	11 / 40 (27.50%)	17 / 40 (42.50%)	12 / 38 (31.58%)
occurrences (all)	18	30	19
More focused			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	3 / 38 (7.89%)
occurrences (all)	1	5	4
More confidence			
subjects affected / exposed	4 / 40 (10.00%)	8 / 40 (20.00%)	5 / 38 (13.16%)
occurrences (all)	5	13	6
Uninterested in others			
subjects affected / exposed	2 / 40 (5.00%)	1 / 40 (2.50%)	1 / 38 (2.63%)
occurrences (all)	4	1	2
Nail biting			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Nausea and/ or vomiting			
subjects affected / exposed	3 / 40 (7.50%)	3 / 40 (7.50%)	3 / 38 (7.89%)
occurrences (all)	4	4	5

Abdominal or stomach pain			
subjects affected / exposed	9 / 40 (22.50%)	8 / 40 (20.00%)	6 / 38 (15.79%)
occurrences (all)	19	10	10
Decreased appetite			
subjects affected / exposed	3 / 40 (7.50%)	2 / 40 (5.00%)	4 / 38 (10.53%)
occurrences (all)	5	3	6
Hungry or increased appetite			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	1 / 38 (2.63%)
occurrences (all)	1	2	1
Constipation			
subjects affected / exposed	5 / 40 (12.50%)	2 / 40 (5.00%)	1 / 38 (2.63%)
occurrences (all)	11	2	1
Diarrhea			
subjects affected / exposed	2 / 40 (5.00%)	1 / 40 (2.50%)	3 / 38 (7.89%)
occurrences (all)	2	2	4
Increased fluid intake			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	4
Respiratory, thoracic and mediastinal disorders			
Coughing			
subjects affected / exposed	4 / 40 (10.00%)	2 / 40 (5.00%)	3 / 38 (7.89%)
occurrences (all)	6	3	5
Coughing up mucus			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Skin rash			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	3 / 38 (7.89%)
occurrences (all)	4	0	4
Renal and urinary disorders			
Bed wetting			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Musculoskeletal and connective tissue disorders			
Muscle pain/ cramps			

subjects affected / exposed	5 / 40 (12.50%)	1 / 40 (2.50%)	5 / 38 (13.16%)
occurrences (all)	8	1	7
Infections and infestations			
Fever			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	0 / 38 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Phase 2 - PL first		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 39 (61.54%)		
Cardiac disorders			
Changes in heart rate or palpitation			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Headache			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	10		
Drowsiness			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	7		
Dry throat/ dry mouth			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	4		
Hoarseness			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Congested nose			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	7		
Sneezing			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Nasal irritation			

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Runny nose			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	5		
Burning sensation in nose and/ or ears			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Insomnia/ sleep difficulties			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Staring/ daydreams			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Sensitive for fragrances			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Eye disorders			
Watery eyes			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Social circumstances			
Less talk to others			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Persistent thoughts and/or feelings			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Irritability / anger			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	7		
Sad			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Prone to crying or more emotional			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Anxious, worried or discomfort			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Happy or satisfied			
subjects affected / exposed	10 / 39 (25.64%)		
occurrences (all)	16		
Euphoric or unusually happy			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Calm, relaxed or comfortable			
subjects affected / exposed	11 / 39 (28.21%)		
occurrences (all)	20		
More focused			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
More confidence			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	10		
Uninterested in others			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Nail biting			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea and/ or vomiting			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Abdominal or stomach pain			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		

Decreased appetite subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6		
Hungry or increased appetite subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Constipation subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0		
Diarrhea subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0		
Increased fluid intake subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 2		
Respiratory, thoracic and mediastinal disorders Coughing subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Coughing up mucus subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0		
Skin and subcutaneous tissue disorders Skin rash subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Renal and urinary disorders Bed wetting subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle pain/ cramps subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Infections and infestations			

Fever subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2020	Reference to the EU Regulation 2016/679 (General Data Protection Regulation) or GDPR (General Data Protection Regulation) and the Belgian Legislation on the protection of natural persons with regard to the processing of personal data on the free movement of such data was added to the protocol.
31 March 2021	Inclusion of more participants in the study: increased from 60 to 80 patients with ASD

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.

The covid pandemic caused some delay (and sometimes loss) of the follow up data.

Notes: