Clinical trial results:
A randomized, open-label, multicenter, phase 2 clinical trial to explore the safety and efficacy of sepranolone in pediatric and adult patients with Tourette Syndrome.

Summary

EudraCT number	2021-001045-12
Trial protocol	DK
Global end of trial date	01 February 2023

Results information

Result version number	v1 (current)
This version publication date	07 July 2023
First version publication date	07 July 2023

Trial information

Trial identification

Sponsor protocol code	APH205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05434546
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Asarina Pharma ApS
Sponsor organisation address	Ole Maaloes vej 3 , Copenhagen, Denmark, 2200
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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	25 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of sepranolone to reduce tic severity in patients with Tourette syndrome at 12 weeks

Protection of trial subjects:

Subjects taking part in this clinical study were insured by the Sponsor against any injury caused by the clinical study, in accordance with the local regulatory requirements. A copy of the insurance certificate was provided to each Investigator and was filed in the investigator's file at the sites and in the clinical trial's Trial Master File (TMF). The Investigator had to notify the Sponsor immediately upon notice of any claims or lawsuits brought by the patients or their relatives.

Background therapy:

Patient's standard of care Tourette treatment for 12 weeks.

Evidence for comparator: -

Actual start date of recruitment	16 February 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	Denmark: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	23
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

4 pediatric patients and 24 adults were screened. All screened patients were randomized except one pediatric patient and one adult who did not fulfill inclusion criteria. Among the pediatric patients, two were randomized to the Sepranolone group and one to the SoC group, while 15 adults were randomized to Sepranolone group and 8 to the SoC group.

Pre-assignment

Screening details:

All subjects who signed the informed consent were enrolled in the study and all clinical data related to these subjects were documented.

Pre-assignment period milestones

Number of subjects started	26
Number of subjects completed	26

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sepranolone + Standard of Care (SoC)

Arm description:

Sepranolone 10 mg subcutaneously twice weekly for 12 weeks alongside the patient's standard of care Tourette treatment.

Arm type	Experimental
Investigational medicinal product name	Sepranolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sepranolone 10 mg sc twice weekly for 12 weeks alongside the patient's standard of care Tourette treatment.

Arm title	Standard of Care (SoC)

Arm description:

Continuation of the patient's standard of care Tourette treatment for 12 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Sepranolone + Standard of Care (SoC)	Standard of Care (SoC)
Started	17	9
Completed	16	8
Not completed	1	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sepranolone + Standard of Care (SoC)
Reporting group description:	
Sepranolone 10 mg subcutaneously twice weekly for 12 weeks alongside the patient's standard of care Tourette treatment.	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Continuation of the patient's standard of care Tourette treatment for 12 weeks.	

Reporting group values	Sepranolone + Standard of Care (SoC)	Standard of Care (SoC)	Total
Number of subjects	17	9	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	1	3
Adults (18-64 years)	15	8	23
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	35	33	
standard deviation	± 8.3	± 10	-
Gender categorical			
All randomized pediatric patients (3/3) were male whereas 5/15 (33.3%) of the adults in the Sepranolone group and 3/8 (37.5%) in the SoC group were female.			
Units: Subjects			
Female	5	3	8
Male	12	6	18

Subject analysis sets	
Subject analysis set title	Sepranolone + SoC. Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Sepranolone Full analysis set (FAS) consisted of all patients in the Sepranolone group who were randomized into the study. The FAS followed the intention-to-treat (ITT) principle, i.e., patients were analyzed in the treatment group to which they were randomized, regardless of whether treatment was received as planned.	
Subject analysis set title	Sepranolone + SoC. mITT analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified intention-to-treat (mITT) analysis set included patients in the FAS who had a valid baseline assessment and had taken at least 6 doses of study drug per 4-week period. The mITT was the primary analysis set for efficacy analyses.

Subject analysis set title	Sepranolone + SoC. Safety analysis set (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAS consisted of all patients who received at least one (1) dose of Sepranolone. Patients were analyzed according to the treatment they actually received. The SAS was the primary analysis set for safety analyses.

Subject analysis set title	SoC. Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS consisted of all patients who were randomized into the study. The FAS followed the intention-to-treat (ITT) principle, i.e., patients were analyzed in the treatment group to which they were randomized, regardless of whether treatment was received as planned.

Subject analysis set title	SoC. mITT analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT analysis set included patients in the FAS who had a valid baseline assessment and had taken at least 6 doses of study drug per 4-week period. The mITT was the primary analysis set for efficacy analyses.

Subject analysis set title	SoC. Safety analysis set (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAS for the SoC group consisted of all patients randomized to the SoC group. Patients were analyzed according to the treatment they actually received. The SAS was the primary analysis set for safety analyses.

Reporting group values	Sepranolone + SoC. Full analysis set (FAS)	Sepranolone + SoC. mITT analysis set	Sepranolone + SoC. Safety analysis set (SAS)
Number of subjects	17	17	17
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	2	2
Adults (18-64 years)	15	15	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
All randomized pediatric patients (3/3) were male whereas 5/15 (33.3%) of the adults in the Sepranolone group and 3/8 (37.5%) in the SoC group were female.			
Units: Subjects			
Female			
Male			

Reporting group values	SoC. Full analysis set (FAS)	SoC. mITT analysis set	SoC. Safety analysis set (SAS)
Number of subjects	9	9	9
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	1	1	1
Adults (18-64 years)	8	8	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
All randomized pediatric patients (3/3) were male whereas 5/15 (33.3%) of the adults in the Sepranolone group and 3/8 (37.5%) in the SoC group were female.			
Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Sepranolone + Standard of Care (SoC)

Reporting group description:

Sepranolone 10 mg subcutaneously twice weekly for 12 weeks alongside the patient's standard of care Tourette treatment.

Reporting group title	Standard of Care (SoC)

Reporting group description:

Continuation of the patient's standard of care Tourette treatment for 12 weeks.

Subject analysis set title	Sepranolone + SoC. Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Sepranolone Full analysis set (FAS) consisted of all patients in the Sepranolone group who were randomized into the study. The FAS followed the intention-to-treat (ITT) principle, i.e., patients were analyzed in the treatment group to which they were randomized, regardless of whether treatment was received as planned.

Subject analysis set title	Sepranolone + SoC. mITT analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified intention-to-treat (mITT) analysis set included patients in the FAS who had a valid baseline assessment and had taken at least 6 doses of study drug per 4-week period. The mITT was the primary analysis set for efficacy analyses.

Subject analysis set title	Sepranolone + SoC. Safety analysis set (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAS consisted of all patients who received at least one (1) dose of Sepranolone. Patients were analyzed according to the treatment they actually received. The SAS was the primary analysis set for safety analyses.

Subject analysis set title	SoC. Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS consisted of all patients who were randomized into the study. The FAS followed the intention-to-treat (ITT) principle, i.e., patients were analyzed in the treatment group to which they were randomized, regardless of whether treatment was received as planned.

Subject analysis set title	SoC. mITT analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT analysis set included patients in the FAS who had a valid baseline assessment and had taken at least 6 doses of study drug per 4-week period. The mITT was the primary analysis set for efficacy analyses.

Subject analysis set title	SoC. Safety analysis set (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAS for the SoC group consisted of all patients randomized to the SoC group. Patients were analyzed according to the treatment they actually received. The SAS was the primary analysis set for safety analyses.

Primary: Change from baseline YGTSS Total Tic Score at week 4, 8 and 12.

End point title	Change from baseline YGTSS Total Tic Score at week 4, 8 and 12.

End point description:

The Yale Global Tic Severity Scale (YGTSS) is a validated scale for assessing the severity of motor and vocal tics in both children and adults with Tourette syndrome. Tics are scored based on a semi-structured interview, including scoring of the number, frequency, intensity, complexity, and interference

of tics. The primary endpoint is the total tic score assessment. The score ranges from 0-50, where a higher score indicates a worse outcome.

End point type	Primary

End point timeframe:

Change from baseline at week 4, 8 and 12.

End point values	Sepranolone + SoC. mITT analysis set	SoC. mITT analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	9		
Units: Change in total score from baseline				
least squares mean (confidence interval 90%)	-8.57 (-11.22 to -5.92)	-3.94 (-7.76 to -0.11)		

Statistical analyses

Statistical analysis title	Change from baseline in YGTSS total tic score

Statistical analysis description:

The change from baseline in Yale Global Tic Severity Scale (YGTSS) total tic score was modelled using mixed model repeated measures (MMRM) analysis with treatment group, visit and treatment by visit interaction as fixed effects, patient as random effect and baseline YGTSS total tic score as covariate. In this model, the statistical hypothesis for the primary objective is evaluated using a one-sided t-test at significance level 5%.

Comparison groups	Sepranolone + SoC. mITT analysis set v SoC. mITT analysis set
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.051
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	-4.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.31
upper limit	0.04

Secondary: Safety and tolerability of Sepranolone in adolescent and adult patients with Tourette syndrome

End point title	Safety and tolerability of Sepranolone in adolescent and adult patients with Tourette syndrome

End point description:

Collection of adverse events (AEs) including spontaneous reporting, number of subjects with clinically significant changes in clinical safety laboratory blood and urine test values, vital signs, weight, and injection related events.

End point type	Secondary

End point timeframe:

From randomization (day 1) until the end of study visit (week 16).

End point values	Sepranolone + SoC. Safety analysis set (SAS)	SoC. Safety analysis set (SAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: Percentage of participants				
number (not applicable)				
Any AEs	94	11		
SAEs	0	0		
AEs leading to death	0	0		
AEs leading to study withdrawal	6	0		
AEs leading to treatment withdrawal	6	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline YGTSS Impairment Score at week 4, 8 and 12.

End point title	Change from baseline YGTSS Impairment Score at week 4, 8 and 12.

End point description:

The Yale Global Tic Severity Scale (YGTSS) is a validated scale for assessing the severity of motor and vocal tics in both children and adults with Tourette syndrome. Tics are scored based on a semistructured interview, including scoring of the number, frequency, intensity, complexity, and interference of tics. The secondary endpoint is the impairment score assessment. The score ranges from 0-50, where a higher score indicates a worse outcome.

End point type	Secondary

End point timeframe:

Change from baseline at week 4, 8 and 12.

End point values	Sepranolone + SoC. mITT analysis set	SoC. mITT analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	9		
Units: Change in impairment score from baseline				
least squares mean (confidence interval 90%)	-4.19 (-8.86 to 0.47)	-0.87 (-7.58 to 5.84)		

Statistical analyses

Statistical analysis title	Change from baseline in the YGTSS impairment score
Comparison groups	Sepranolone + SoC. mITT analysis set v SoC. mITT analysis set
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.246
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.5
upper limit	4.85

Notes:

[1] - The change from baseline YGTSS impairment score at week 4, 8, and 12 was modelled using the same Mixed Model Repeated Measures (MMRM) as YGTSS total score but with baseline YGTSS impairment score as baseline. The Least Squares (LS) means for each treatment as well as the treatment difference from the model at each time point was tabulated and visualised along with the 90% two-sided confidence interval.

Secondary: Change from baseline PUTS score at week 4, 8 and 12

End point title	Change from baseline PUTS score at week 4, 8 and 12

End point description:

The Premonitory Urge for Tics Scale (PUTS) scale is an assessment aiming to quantify the premonitory urge to tic. The scale is reliable and valid instrument for children from above the age of 10 and for adults. This scale is used as a self-report assessment instrument, where the Investigator asks 10 questions, out of which the score for the first 9 questions add up to the total score (i.e., the 9-Item Total). The respondent has 4 alternatives, "not at all true", "a little true", "pretty much true" and "very much true," represented by a score or 1-4, respectively. The total score ranges from 9-36, where a higher score indicates a worse outcome.

End point type	Secondary

End point timeframe:

Change from baseline at week 4, 8 and 12.

End point values	Sepranolone + SoC. mITT analysis set	SoC. mITT analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	9		
Units: Change in score from baseline				
least squares mean (confidence interval 90%)	-2.60 (-4.36 to -0.84)	-1.80 (-4.33 to 0.74)		

Statistical analyses

Statistical analysis title	Change in baseline in PUTS score

Statistical analysis description:

The change from baseline in 9-item total PUTS score at week 4, 8, and 12 was modelled using mixed model repeated measures (MMRM) with baseline total PUTS score as covariate. The Least Squares (LS) means for each treatment as well as the treatment difference from the model at each time point was tabulated and visualised along with the 90% twosided confidence interval.

Comparison groups	Sepranolone + SoC. mITT analysis set v SoC. mITT analysis set
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.333
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.94
upper limit	2.33

Secondary: Change from baseline in GTS-QOL physical/ADL subscale at week 4, 8 and 12

End point title	Change from baseline in GTS-QOL physical/ADL subscale at week 4, 8 and 12

End point description:

The Gilles de la Tourette Syndrome - Quality of Life (GTS-QoL) physical/activities of daily living (ADL) subscale assesses the impact of the symptoms of Tourette syndrome on the subject's quality of life. The instrument consists of 27 questions, asked by an interviewer, where subjects score the extent of impact on a 5-point verbal scale ranging from "no problems" to "extreme problems." The score ranges from 27-135, where a higher score indicates a worse outcome.

End point type	Secondary

End point timeframe:

Change from baseline at week 4, 8 and 12.

End point values	Sepranolone + SoC. mITT analysis set	SoC. mITT analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	9		
Units: Change in score from baseline				
least squares mean (confidence interval 90%)	-2.91 (-4.34 to 1.49)	-2.21 (-4.25 to -0.16)		

Statistical analyses

Statistical analysis title	Change in Baseline in the GTS-QoL ADL Subscale.

Statistical analysis description:

The change from baseline in the Gilles de la Tourette Syndrome - Quality of Life (GTS-QOL) total score and physical/activities of daily living (ADL) subscale at week 4, 8, and 12 will be modelled using the same MMRM as YGTSS but with baseline total GTS-QoL score/baseline of the ADL
subscale as covariate. The LS means for each treatment as well as the treatment difference from the model at each time point will be tabulated and
visualised along with the 90% two-sided confidence.

Comparison groups	Sepranolone + SoC. mITT analysis set v SoC. mITT analysis set
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.316
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.2
upper limit	1.79

Secondary: TS-CGI score at week 4, 8 and 12

End point title	TS-CGI score at week 4, 8 and 12

End point description:

The Tourette Syndrome-Clinical Global Impression (TS-CGI) is a clinician rating of the change in severity of the symptoms of Tourette syndrome. The scale is a 7-step Likert scale, where the following alternatives are represented by a score of 1-7, respectively: "very much worsened," "much worsened," "minimally worsened," "no change," "minimally improved," "much improved," or "very much improved." The score ranges from 1-7, where a higher score indicates a better outcome.

End point type	Secondary

End point timeframe:

TS-CGI score at week 4, 8 and 12.

End point values	Sepranolone + SoC. mITT analysis set	SoC. mITT analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	9		
Units: Percentage of improved participants				
number (not applicable)	50.0	37.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: The reporting of AEs started after randomization and continued until visit 7, i.e. the Follow-up visit.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	Sepranolone
Reporting group description: -	
Reporting group title	No Intervention
Reporting group description: -	

Serious adverse events	Sepranolone	No Intervention	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Sepranolone	No Intervention	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)	1 / 9 (11.11%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Illness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Injection site bruising			
subjects affected / exposed	5 / 17 (29.41%)	0 / 9 (0.00%)	
occurrences (all)	7	0	
Injection site erythema			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Injection site induration			
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Injection site pain			
subjects affected / exposed	9 / 17 (52.94%)	0 / 9 (0.00%)	
occurrences (all)	12	0	
Injection site pruritus			
subjects affected / exposed	6 / 17 (35.29%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Injection site swelling			
subjects affected / exposed	9 / 17 (52.94%)	0 / 9 (0.00%)	
occurrences (all)	16	0	
Psychiatric disorders			
Mood altered			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Influenza			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	2	2	
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported