Clinical trial results:
A Multi-center, Randomized, Double Blind, Placebo Controlled Phase 2 Study of the Efficacy, Safety and Tolerability of RO5186582 in Adults and Adolescents with Down Syndrome (CLEMATIS).

Summary

EudraCT number	2013-001263-23
Trial protocol	GB ES IT
Global end of trial date	04 May 2016

Results information

Result version number	v1 (current)
This version publication date	20 November 2016
First version publication date	20 November 2016

Trial information

Trial identification

Sponsor protocol code	BP27832

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02024789
WHO universal trial number (UTN)	U1111-1150-1189

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001506-PIP02-14
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	04 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of 26 weeks of treatment with basmisanil (RG1662, RO5186582) on a composite endpoint derived from clinically meaningful responses in working memory and on the level of independent functioning/adaptive behavior or global improvement as compared to placebo.

Protection of trial subjects:

All study subjects/subjects' legally authorized representatives and caregivers were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2014
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	Spain: 47
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	United States: 77
Worldwide total number of subjects	170
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)	0
Adolescents (12-17 years)	85
Adults (18-64 years)	85
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 239 subjects were screened for entry into the study of whom 66 failed screening. A total of 173 subjects were randomized. Three subjects were randomized in error and were withdrawn before receiving any study treatment. A total of 170 subjects were in the study and received at least one dose of study medication.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with matching placebo for 26 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Granules
Routes of administration	Oral use

Dosage and administration details:

Tablet or granule formulation was chosen by each subject at time of randomisation. Matching placebo was administered orally twice daily for 26 weeks.

Arm title	Basmisanil 120 mg (80 mg) bid

Arm description:

Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 120 milligrams (80 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Basmisanil
Investigational medicinal product code	
Other name	RG1662, RO5186582
Pharmaceutical forms	Tablet, Granules
Routes of administration	Oral use

Dosage and administration details:

Tablet or granule formulation was chosen by each subject at time of randomisation. 120 mg (80 mg dosage for subjects 12-13 years old) basmisanil was administered orally twice daily for 26 weeks.

Arm title	Basmisanil 240 mg (160 mg) bid

Arm description:

Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 240 milligrams (160 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks.

Arm type	Experimental

Investigational medicinal product name	Basmisanil
Investigational medicinal product code	
Other name	RG1662, RO5186582
Pharmaceutical forms	Tablet, Granules
Routes of administration	Oral use

Dosage and administration details:

Tablet or granule formulation was chosen by each subject at time of randomisation. 240 mg (160 mg dosage for subjects 12-13 years old) basmisanil was administered orally twice daily for 26 weeks.

Number of subjects in period 1	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid
Started	58	55	57
Completed	54	52	49
Not completed	4	3	8
Adverse event	-	1	3
Unspecified	1	1	3
Withdrawal by sponsor	1	-	-
Withdrawal by subject	2	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with matching placebo for 26 weeks.	
Reporting group title	Basmisanil 120 mg (80 mg) bid
Reporting group description:	
Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 120 milligrams (80 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks.	
Reporting group title	Basmisanil 240 mg (160 mg) bid
Reporting group description:	
Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 240 milligrams (160 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks.	

Reporting group values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid
Number of subjects	58	55	57
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	18.7	18.3	18.7
standard deviation	± 5.2	± 4.9	± 5.4
Gender categorical			
Units: Subjects			
Female	25	23	19
Male	33	32	38

Reporting group values	Total		
Number of subjects	170		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	67		
Male	103		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with matching placebo for 26 weeks.	
Reporting group title	Basmisanil 120 mg (80 mg) bid
Reporting group description:	
Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 120 milligrams (80 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks.	
Reporting group title	Basmisanil 240 mg (160 mg) bid
Reporting group description:	
Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 240 milligrams (160 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks.	

Primary: Percentage of Responders

End point title	Percentage of Responders
End point description:	
The endpoint was derived from responses in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Vineland Adaptive Behavior Scale (VABS) or global improvement Clinical Global Impression (CGI). A subject was a responder if (s)he had a relevant improvement from baseline in at least 2 out of 3 RBANS tasks (change of at least 2 points in List Learning, change of at least 1 point in List Learning and/or List Recall) as well as an increase from baseline in VABS composite score of >/=7 or a final assessment of CGI-Improvement (CGI-I) </= 3. Changes in VABS composite score and final CGI-I had to be consistent per individual. The modified intent-to-treat (mITT) population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The per protocol (PP) population reported here was the mITT population excluding subjects with major protocol violations.	
End point type	Primary
End point timeframe:	
Week 26	

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	46	44	
Units: percentage of responders				
number (not applicable)	29.4	19.6	25	

Statistical analyses

Statistical analysis title	Basmisanil arms versus placebo

Statistical analysis description:

The difference in the percentage of responders between treatment groups was analyzed by means of a logistic regression model.

Comparison groups	Placebo v Basmisanil 120 mg (80 mg) bid v Basmisanil 240 mg (160 mg) bid
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.262
Method	Regression, Logistic

Secondary: Change From Baseline of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) List Learning, List Recognition and List Recall at Week 26

End point title	Change From Baseline of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) List Learning, List Recognition and List Recall at Week 26

End point description:

The following 3 subtests of the RBANS were used: List Learning (score range 0-40), List Recognition (score range 0-20) and List Recall (score range 0-10). Higher scores indicate better cognitive function. A positive change from baseline indicates an improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[1]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
List learning baseline (n=57, 50, 53)	15.26 (± 7.21)	14.34 (± 6.91)	16.19 (± 6.54)	
List learning change from baseline (n=51, 47, 44)	3.14 (± 6.06)	2.72 (± 6.15)	2.36 (± 4.77)	
List recognition baseline (n=57, 50, 53)	15.65 (± 4.12)	15.52 (± 3.9)	15.32 (± 4.45)	
List recog change from baseline (n=51, 47, 44)	1.24 (± 3.24)	1.38 (± 3.08)	1.8 (± 3.92)	
List recall baseline (n=57, 50, 53)	2.68 (± 3.04)	2.64 (± 2.66)	2.87 (± 3.03)	
List recall change from baseline (n=51, 47, 44)	0.27 (± 2.37)	0.21 (± 3.13)	-0.07 (± 2.4)	

Notes:

[1] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Vineland Adaptive Behavior Scale (VABS) Composite Score at Week 26

End point title	Change From Baseline of Vineland Adaptive Behavior Scale (VABS) Composite Score at Week 26

End point description:

The VABS-version II measures personal and social skills such as communication, daily living skills, and socialization and provides a composite score reflecting an individual's overall function. The survey interview form was used and administered to parents or caregivers using a semi-structured interview format. Reported here is the global score (adaptive behaviors composite). Higher scores indicate a higher level of function. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[2]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=56, 50, 53)	62.14 (± 12.82)	62.02 (± 12.45)	62.79 (± 10.63)	
Change from baseline (n=50, 46, 43)	2.42 (± 10.15)	2 (± 4.02)	2.02 (± 4.55)	

Notes:

[2] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression-Improvement (CGI-I) Score

End point title	Clinical Global Impression-Improvement (CGI-I) Score

End point description:

The CGI-I is a 7-point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention, and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. Score ranges from 1-7 with a lower score indicating an improved outcome relative to baseline. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	47	46	
Units: units on a scale				
arithmetic mean (standard deviation)	3.12 (± 0.75)	3.28 (± 0.85)	3.5 (± 0.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of RBANS Story Memory, Picture Naming, Semantic Fluency and Digit Span at Week 26

End point title	Change From Baseline of RBANS Story Memory, Picture Naming, Semantic Fluency and Digit Span at Week 26

End point description:

The following 4 subtests of the RBANS were evaluated: story memory (score range 0-12), picture naming (score range 0-10), semantic fluency (score range 0-40) and digit span (score range 0-16). Higher scores indicate better cognitive function. A positive change from baseline indicates an improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[3]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
Story memory baseline (n=57, 50, 53)	6.16 (± 4.68)	5.78 (± 4.06)	6.47 (± 4.31)	
Story memory change from baseline (n=51, 47, 44)	-0.25 (± 2.86)	-0.94 (± 3.44)	-0.8 (± 2.92)	
Picture naming baseline (n=57, 50, 53)	6.74 (± 1.75)	7.04 (± 1.64)	7.08 (± 1.47)	
Picture naming change from baseline (n=51, 47, 44)	-0.53 (± 1.45)	-1.02 (± 1.81)	-1.02 (± 1.5)	
Semantic fluency baseline (n=57, 50, 53)	8.05 (± 3.92)	8.92 (± 4.3)	8.6 (± 3.9)	
Semantic fl. change from baseline (n=51, 47, 44)	-0.51 (± 3.48)	-1.21 (± 3.62)	-1 (± 3.6)	
Digit span baseline (n=57, 50, 53)	4.26 (± 1.95)	3.58 (± 1.89)	3.98 (± 1.7)	
Digit span change from baseline (n=51, 47, 44)	0.02 (± 1.32)	0.28 (± 1.56)	0.18 (± 1.76)	

Notes:

[3] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of VABS Domain Standardised Scores (Communication, Socialisation, Daily Living Skills) at Week 26

End point title	Change From Baseline of VABS Domain Standardised Scores (Communication, Socialisation, Daily Living Skills) at Week 26

End point description:

Reported here are the VABS domain standardised scores (communication, socialisation, daily living skills). Higher scores indicate a higher level of function. A positive change from baseline indicates an improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[4]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
Communication baseline (n=56, 50, 53)	59.34 (± 17.91)	57.42 (± 15.9)	59.17 (± 17.55)	
Communication change from baseline (n=50, 46, 43)	2.58 (± 14.36)	4.57 (± 8.42)	1.86 (± 6.83)	
Socialisation baseline (n=56, 50, 53)	70.52 (± 13.94)	70.32 (± 14.53)	70.7 (± 12.72)	
Socialisation change from baseline (n=50, 46, 43)	2.46 (± 11.28)	0.57 (± 7.02)	2.12 (± 7.1)	
Daily living skills baseline (n=56, 50, 53)	61.96 (± 10.63)	62.78 (± 10.93)	63.7 (± 9.21)	
Daily living change from baseline (n=50, 46, 43)	2.52 (± 9.24)	1.22 (± 4.35)	1.79 (± 5.01)	

Notes:

[4] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Rivermead Behavioral Memory Test Children's Version (RBMT-C) Subtest Endpoints at Week 26

End point title	Change From Baseline of Rivermead Behavioral Memory Test Children's Version (RBMT-C) Subtest Endpoints at Week 26

End point description:

The RBMT-C comprises a number of subtests, each attempting to provide an objective measure of a range of everyday memory problems reported and observed in subjects with memory difficulties. Subtests analysed include 1 Delayed route recall (score range: 0-5), 2 Delayed story total (0.0-62.0), 3 Immediate story total (0.0-62.0), 4 Orientation questions (0.0-11.0), 5 Remembering a name (0-4), 6 Remembering a short route (0-5), 7 Remembering the appointment (0-2), 8 Remembering the

belonging (0-4), 9 Remembering to deliver a message 1 (0-3), 10 Remembering to deliver a message 2 (0-3), 11 Test face recognition (0-5), and 12 Test for picture recognition (0-10). A positive change from baseline indicates improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[5]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
1 Delayed route recall baseline (n=57, 50, 53)	3.72 (± 1.7)	3.74 (± 1.68)	3.83 (± 1.37)	
1 Delayed route change from baseline (n=51,47,44)	-0.27 (± 1.96)	-0.62 (± 1.91)	-0.25 (± 1.66)	
2 Delayed story baseline (n=57, 50, 53)	8.29 (± 5.36)	7.99 (± 5.65)	8.42 (± 5.12)	
2 Delayed story change from baseline (n=51,47,44)	0.27 (± 3.06)	-0.52 (± 4.42)	-0.77 (± 3.86)	
3 Immediate story baseline (n=57, 50, 53)	8.91 (± 6)	8.27 (± 5.89)	8.98 (± 5.54)	
3 Imm story change from baseline (n=51, 47, 44)	0.02 (± 2.63)	-0.15 (± 3.38)	-1.27 (± 4.19)	
4 Orientation questions baseline (n=55, 49, 51)	7.35 (± 2.62)	7.09 (± 2.34)	7.67 (± 2.4)	
4 Orient quest change from baseline (n=49, 46, 42)	0.11 (± 1.91)	-0.17 (± 1.92)	0.18 (± 1.71)	
5 Remembering name baseline (n=57, 50, 53)	2.3 (± 1.48)	2.18 (± 1.38)	1.91 (± 1.5)	
5 Remem name change from baseline (n=51, 47, 44)	-0.02 (± 1.85)	0 (± 1.66)	0 (± 1.79)	
6 Remembering short route baseline (n=57, 50, 53)	3.77 (± 1.51)	3.98 (± 1.39)	3.79 (± 1.5)	
6 Remem route change from baseline (n=51, 47, 44)	-0.12 (± 1.89)	-0.68 (± 1.84)	-0.11 (± 1.6)	
7 Remembering appointment baseline (n=57, 50, 53)	0.96 (± 0.78)	0.92 (± 0.7)	1.09 (± 0.71)	
7 Remem apptmt change from baseline (n=51, 47, 44)	0.43 (± 0.78)	0.49 (± 0.86)	0.23 (± 0.8)	
8 Remembering belonging baseline (n=57, 50, 52)	2.32 (± 1.34)	2.3 (± 1.3)	2.44 (± 1.13)	
8 Remem belong change from baseline (n=50, 47, 43)	0.48 (± 1.23)	0.57 (± 1.28)	0.4 (± 1.59)	
9 Remembering deliver m 1 baseline (n=57, 50, 53)	2.44 (± 0.76)	2.14 (± 0.93)	2.38 (± 0.84)	
9 Remem m 1 change from baseline (n=51, 47, 44)	-0.14 (± 0.96)	0.19 (± 1.01)	0.25 (± 0.92)	
10 Remembering deliver m 2 baseline (n=57, 50, 53)	2.38 (± 0.85)	2.28 (± 0.88)	2.53 (± 0.93)	
10 Remem m 2 change from baseline (n=51, 47, 44)	-0.02 (± 1.19)	0 (± 0.91)	-0.07 (± 1.17)	
11 Face recognition baseline (n=57, 50, 53)	3.04 (± 2.08)	3.08 (± 2.03)	2.96 (± 2.03)	

11 Face recog change from baseline (n=51, 47, 44)	0.02 (± 2.02)	0.15 (± 1.55)	-0.02 (± 1.96)	
12 Pic recognition baseline (n=57, 50, 53)	6.44 (± 4.33)	6.68 (± 3.63)	6.7 (± 3.49)	
12 Pic recog change from baseline (n=50, 47, 44)	0.52 (± 3.8)	-0.04 (± 3)	0.64 (± 3.05)	

Notes:

[5] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Clinical Evaluation of Language Fundamentals (CELF)-4 Subtest Endpoints at Week 26

End point title	Change From Baseline of Clinical Evaluation of Language Fundamentals (CELF)-4 Subtest Endpoints at Week 26

End point description:

CELF-4 subtests test language skills (ages 5 through 21). The Word Classes I subtest gives information about subject's development of categorisation skills and ability to associate word meanings. If the subject was able to perform the Word Classes 1 (score range: 0-42) from the CELF-4 version without any zero scores on the receptive part of 7 consecutive items (i.e., reaching the ceiling of performance on the test), then the Word Classes 2 subtest (score range: 0-42) was used. The subtest Concepts and Following Directions (score range: 0-54; Con follow dir) was used to assess the capacity to follow spoken direction. Higher scores indicate better language skills. A positive change from baseline indicates improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[6]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
Word classes I baseline (n=57, 50, 53)	24.89 (± 9.36)	24.76 (± 7.51)	24.51 (± 9.47)	
Word classes I change from baseline (n=51, 46, 44)	1.69 (± 5.97)	0.24 (± 6.59)	2.75 (± 5.84)	
Word classes 2 baseline (n=54, 45, 49)	5.35 (± 6.27)	4.42 (± 4.96)	4.27 (± 4.81)	
Word classes 2 change from baseline (n=47, 41, 40)	-0.13 (± 5.88)	-0.07 (± 4.29)	0.38 (± 3.54)	
Conc and follow dir baseline (n=57, 49, 53)	14.02 (± 11.11)	14.63 (± 10.64)	15.45 (± 11.95)	
Con follow dir change from baseline (n=51, 45, 44)	0.86 (± 7.2)	0.22 (± 7.65)	-1.25 (± 6.02)	

Notes:

[6] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Observer Memory Questionnaire-Parent Form (OMQ-PF) Total Score at Week 26

End point title	Change From Baseline of Observer Memory Questionnaire-Parent Form (OMQ-PF) Total Score at Week 26

End point description:

The Observer Memory Questionnaire-Parent Form (OMQ-PF) is a 27-item questionnaire designed to ascertain parental perceptions about their child's memory function. All items are rated on a 5-point Likert scale (from 1=strongly agree to 5=strongly disagree, or 1=never to 5=always). Score range is 27-135 with higher scores indicating higher level of function. A positive change from baseline indicates improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was defined as the mITT excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[7]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57, 47, 50)	88.51 (± 16.25)	91.62 (± 17.32)	90.2 (± 15.01)	
Change from baseline (n=49, 42, 40)	6.67 (± 12.93)	2.81 (± 10.43)	5.35 (± 10.9)	

Notes:

[7] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Behavior Rating Inventory of Executive Function Preschool (BRIEF-P) Endpoints at Week 26

End point title	Change From Baseline of Behavior Rating Inventory of Executive Function Preschool (BRIEF-P) Endpoints at Week 26

End point description:

The BRIEF-P is a questionnaire of everyday skills reflective of abilities in the executive domain. Scores were derived for the following scales: Emergent Metacognition Index (EMI; score range 27-81), Emotional Control (EC; 10-30), Flexibility Index (FI; 20-60), Global Executive Composite (GEC; 63-189), Inhibitory Self-Control Index (ISCI; 26-78), Inconsistency (0-20), Inhibit (16-48), Negativity (0-10), Plan/Organize (P/O; 10-30), Shift (10-30) and Working Memory (WM; 17-51). Lower scores indicate higher level of function. A negative change from baseline indicates improvement. The mITT population included all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment. The PP population reported here was the mITT population excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:
Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[8]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
EMI at baseline (n=57, 50, 52)	46.07 (± 8.74)	47.42 (± 9.66)	46.65 (± 9.16)	
EMI change from baseline (n=51, 46, 42)	-2.49 (± 6.22)	-3.52 (± 6.7)	-4.45 (± 6.55)	
EC at baseline (n=57, 50, 52)	13.32 (± 3.47)	14.54 (± 3.32)	14.52 (± 4.11)	
EC change from baseline (n=51, 46, 42)	0 (± 2.36)	-1.46 (± 2.6)	-0.52 (± 3.01)	
FI at baseline (n=57, 50, 52)	28.6 (± 6.6)	31 (± 6.64)	30.08 (± 7.56)	
FI change from baseline (n=51, 46, 42)	-0.39 (± 4.35)	-2.74 (± 4.36)	-1.88 (± 4.4)	
GEC at baseline (n=57, 50, 52)	100.19 (± 17.47)	104.16 (± 18.69)	102.33 (± 20.54)	
GEC change from baseline (n=51, 46, 42)	-4.14 (± 12.17)	-7.87 (± 12.57)	-7.88 (± 12.69)	
ISCI at baseline (n=57, 50, 52)	38.84 (± 8.1)	40.28 (± 7.91)	40.12 (± 9.3)	
ISCI change from baseline (n=51, 46, 42)	-1.25 (± 5.23)	-3.07 (± 6.13)	-2.07 (± 6.09)	
Inconsistency at baseline (n=57, 50, 52)	3.4 (± 1.99)	3.34 (± 2.17)	3.44 (± 2.35)	
Inconsist. change from baseline (n=51, 46, 42)	-0.63 (± 1.88)	-0.43 (± 2.65)	-0.4 (± 1.84)	
Inhibit at baseline (n=57, 50, 52)	25.53 (± 5.4)	25.74 (± 5.31)	25.6 (± 5.86)	
Inhibit change from baseline (n=51, 46, 42)	-1.25 (± 3.5)	-1.61 (± 4.25)	-1.55 (± 3.87)	
Negativity at baseline (n=57, 50, 52)	1.49 (± 1.95)	1.18 (± 1.78)	1.1 (± 1.66)	
Negativity change from baseline (n=51, 46, 42)	-0.41 (± 2.62)	-0.39 (± 2.29)	-0.31 (± 1.88)	
Plan/Organize at baseline (n=57, 50, 52)	16.61 (± 3.36)	16.92 (± 3.7)	16.83 (± 3.7)	
P/O change from baseline (n=51, 46, 42)	-0.76 (± 2.8)	-1.07 (± 2.75)	-1.48 (± 2.42)	
Shift at baseline (n=57, 50, 52)	15.28 (± 3.81)	16.46 (± 4.08)	15.56 (± 3.88)	
Shift change from baseline (n=51, 46, 42)	-0.39 (± 2.97)	-1.28 (± 3.07)	-1.36 (± 1.94)	
Working Memory at baseline (n=57, 50, 52)	29.46 (± 5.91)	30.5 (± 6.51)	29.83 (± 5.97)	
WM change from baseline (n=51, 46, 42)	-1.73 (± 4.17)	-2.46 (± 4.7)	-2.98 (± 4.84)	

Notes:
[8] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Pediatric Quality of Life Inventory (PedsQL)

Cognitive Functioning Scale Scores and the PedsQL Generic Core Scale at Week 26

End point title	Change From Baseline of Pediatric Quality of Life Inventory (PedsQL) Cognitive Functioning Scale Scores and the PedsQL Generic Core Scale at Week 26

End point description:

PedsQL integrates generic and disease-specific instruments. Two modules were used; 1) the Cognitive Functioning Scale (CFS), containing 6 items and 2) the Generic and Cognitive Module (GCM) consisting of 23 items encompassing 4 core domains: Physical Functioning (8 items); Emotional Functioning (5 items); Social Functioning (5 items); School Functioning (5 items). Both modules use a 5-point Likert-type response scale (0 = never a problem to 4 = almost always a problem). The items of the PedsQL modules are reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better outcomes (e.g., less negative impact). A positive change from baseline indicates an improvement. The PP population reported here was the mITT population (all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment) excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[9]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
CFS at baseline (n=57, 49, 52)	54.17 (± 22.75)	60.71 (± 25.1)	59.05 (± 19.85)	
CFS change from baseline (n=51, 46, 42)	10.95 (± 20.43)	7.07 (± 16.64)	12.2 (± 17.62)	
GCM at baseline (n=57, 50, 52)	77.21 (± 14.53)	74.78 (± 15.61)	77.8 (± 14.57)	
GCM change from baseline (n=47, 46, 41)	1.71 (± 12.67)	5.58 (± 12.52)	3.53 (± 9.73)	

Notes:

[9] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of PedsQL Family Impact Scale Score at Week 26

End point title	Change From Baseline of PedsQL Family Impact Scale Score at Week 26

End point description:

Caregivers completed the PedsQL Family Impact Module version 2 to measure the impact on a parent of caring for a subject with an acute or chronic condition. It encompasses 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items), 5) Communication (3 items), 6) Worry (5 items), 7) Daily Activities (3 items) and 8) Family Relationships (5 items). For each item a 5-point response scale is utilized (0 = never a problem to 4 = always a problem). The PedsQL module is reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate less negative impact. A positive change from baseline indicates improvement. The PP population reported was the mITT population (all subjects randomised, who received at least one dose of double-blind study medication and provided at least one post dose assessment) excluding subjects with major protocol violations.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57[10]	51	55	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57, 49, 51)	75.87 (± 15.52)	77.75 (± 16.17)	78.62 (± 13.2)	
Change from baseline (n=50, 46, 41)	4.43 (± 12.38)	2.23 (± 12.55)	5.03 (± 11.48)	

Notes:

[10] - Here, n in the subcategory title is the number of subjects analysed for each arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects with Adverse Events

End point title	Safety: Percentage of Subjects with Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety analysis population includes all subjects who received at least one dose of the study medication, whether prematurely withdrawn from the study or not. For the safety population analysis, data are analysed according to treatment actually taken.

End point type	Secondary

End point timeframe:

Up to Week 32

End point values	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	55	57	
Units: percentage of subjects				
number (not applicable)	77.6	70.9	75.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Basmisanil Plasma Concentrations

End point title	Pharmacokinetics: Basmisanil Plasma Concentrations[11]

End point description:

Pharmacokinetic (PK) population included those subjects who were evaluated for plasma concentration. Here, n in the subcategory title is the number of subjects analysed in each arm.

End point type	Secondary

End point timeframe:

Day 1 at 0.5 hours (hr), 2 hr, 4 hr, 6 hr, Day 14 predose, Day 14, 2 hr, 4 hr, 6 hr, Day 42 predose, 2 hr, 4 hr, 6 hr, Day 84 predose, Day 140 and Day 182

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Basmisanil concentrations were not measured in the placebo arm as these subjects did not receive basmisanil treatment.

End point values	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: nanograms/millilitre (ng/ml)				
arithmetic mean (standard deviation)				
Day 1 at 0.5 hr (n=10, 10)	130.33 (± 235.87)	243.45 (± 259.89)		
Day 1 at 2 hr (n=9, 11)	921.56 (± 422.18)	1377.09 (± 889.56)		
Day 1 at 4 hr (n=9, 11)	1125.89 (± 427.69)	1594.36 (± 849.8)		
Day 1 at 6 hr (n=9, 11)	998.44 (± 397.57)	1356.55 (± 624.02)		
Day 14 predose (n=49, 53)	1755.45 (± 856.61)	2515.4 (± 1031.84)		
Day 14 (n=39, 43)	2240.41 (± 999.21)	2992.58 (± 1275.82)		
Day 14 at 2 hr (n=10, 12)	2130 (± 769.76)	3202.5 (± 1105.77)		
Day 14 at 4 hr (n=10, 11)	2065 (± 714.43)	3481.82 (± 1347.38)		
Day 14 at 6 hr (n=10, 11)	1705.3 (± 614.86)	3077.27 (± 1440.69)		
Day 42 predose (n=52, 53)	1679.9 (± 898.58)	2689.25 (± 1048.54)		
Day 42 at 2 hr (n=10, 10)	2143.8 (± 606.81)	3631 (± 1248.09)		
Day 42 at 4 hr (n=10, 10)	2222.1 (± 700.6)	3718 (± 1390.5)		
Day 42 at 6 hr (n=10, 9)	1990.5 (± 633.37)	3026.67 (± 1286.8)		
Day 84 predose (n=52, 50)	1572.96 (± 796.26)	2868.98 (± 1642.28)		
Day 140 (n=50, 47)	1709.54 (± 671.96)	2710.64 (± 1438.87)		
Day 182 (n=47, 45)	1575.98 (± 870.34)	2672.29 (± 1437.32)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to end of treatment (EOT) at Week 26 and up to follow-up visit 2 four to six weeks after EOT (Weeks 30-32).

Adverse event reporting additional description:

The safety analysis population included all subjects who received at least one dose of the study medication, whether prematurely withdrawn from the study or not. For the safety population analysis, data were analyzed according to treatment actually taken.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with matching placebo for 26 weeks. Follow-up visit 1 was one week after end of treatment (EOT) and follow-up visit 2 was four to six weeks after EOT.

Reporting group title	Basmisanil 120 mg (80 mg) bid

Reporting group description:

Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 120 milligrams (80 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks. Follow-up visit 1 was one week after end of treatment (EOT) and follow-up visit 2 was four to six weeks after EOT.

Reporting group title	Basmisanil 240 mg (160 mg) bid

Reporting group description:

Male and female subjects 12−30 years of age (inclusive) with Down syndrome were treated with 240 milligrams (160 mg dosage for subjects 12-13 years old) basmisanil for 26 weeks. Follow-up visit 1 was one week after end of treatment (EOT) and follow-up visit 2 was four to six weeks after EOT.

Serious adverse events	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 58 (1.72%)	2 / 55 (3.64%)	2 / 57 (3.51%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Nervous system disorders			
Altered state of consiousness			

subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Salmonellosis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 55 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Basmisanil 120 mg (80 mg) bid	Basmisanil 240 mg (160 mg) bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 58 (56.90%)	28 / 55 (50.91%)	31 / 57 (54.39%)
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 58 (0.00%)	3 / 55 (5.45%)	1 / 57 (1.75%)
occurrences (all)	0	3	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 58 (3.45%)	1 / 55 (1.82%)	4 / 57 (7.02%)
occurrences (all)	3	2	4
Headache			
subjects affected / exposed	8 / 58 (13.79%)	10 / 55 (18.18%)	7 / 57 (12.28%)
occurrences (all)	10	16	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 58 (0.00%)	3 / 55 (5.45%)	1 / 57 (1.75%)
occurrences (all)	0	3	1
Pyrexia			

subjects affected / exposed	3 / 58 (5.17%)	2 / 55 (3.64%)	4 / 57 (7.02%)
occurrences (all)	3	2	4
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	3 / 58 (5.17%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences (all)	3	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 58 (5.17%)	3 / 55 (5.45%)	2 / 57 (3.51%)
occurrences (all)	3	6	2
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	2 / 55 (3.64%)	3 / 57 (5.26%)
occurrences (all)	0	2	3
Diarrhoea			
subjects affected / exposed	5 / 58 (8.62%)	2 / 55 (3.64%)	2 / 57 (3.51%)
occurrences (all)	8	2	2
Nausea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	3 / 57 (5.26%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	7 / 58 (12.07%)	3 / 55 (5.45%)	5 / 57 (8.77%)
occurrences (all)	9	3	5
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 58 (0.00%)	3 / 55 (5.45%)	0 / 57 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 55 (0.00%)	3 / 57 (5.26%)
occurrences (all)	2	0	4
Ear infection			
subjects affected / exposed	0 / 58 (0.00%)	3 / 55 (5.45%)	1 / 57 (1.75%)
occurrences (all)	0	3	1
Furuncle			
subjects affected / exposed	0 / 58 (0.00%)	2 / 55 (3.64%)	3 / 57 (5.26%)
occurrences (all)	0	2	6

Gastroenteritis			
subjects affected / exposed	3 / 58 (5.17%)	5 / 55 (9.09%)	1 / 57 (1.75%)
occurrences (all)	3	7	2
Gastroenteritis viral			
subjects affected / exposed	3 / 58 (5.17%)	2 / 55 (3.64%)	0 / 57 (0.00%)
occurrences (all)	3	2	0
Nasopharyngitis			
subjects affected / exposed	7 / 58 (12.07%)	3 / 55 (5.45%)	4 / 57 (7.02%)
occurrences (all)	10	3	4
Onychomycosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	3 / 57 (5.26%)
occurrences (all)	1	0	3
Otitis externa			
subjects affected / exposed	3 / 58 (5.17%)	2 / 55 (3.64%)	2 / 57 (3.51%)
occurrences (all)	3	2	2
Upper respiratory tract infection			
subjects affected / exposed	12 / 58 (20.69%)	7 / 55 (12.73%)	9 / 57 (15.79%)
occurrences (all)	20	13	11
Viral infection			
subjects affected / exposed	3 / 58 (5.17%)	1 / 55 (1.82%)	2 / 57 (3.51%)
occurrences (all)	3	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2014	In the inclusion criterion "Ability to complete the Clinical Evaluation of Language Fundamentals (CELF)−preschool 2 Word Classes task" the score was decreased from 7 to 4 for the adolescents. The coagulation test was performed at screening only as there was no rationale to monitor coagulation parameters throughout the study. In the Body-mass Index (BMI) criterion the upper end of the range was changed from 30 to 32 kg/m^2 for adolescents.
27 April 2015	The post-trial access to basmisanil was updated in accordance with Roche Global Policy on Continued Access to investigational medicinal products (IMPs). Exclusion criteria were revised to incorporate subjects with International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis in the study. Updates were made to allow for repeat testing in the event of laboratory test abnormalities to confirm results and prevent unnecessary screen failures. For serum creatinine, it was clarified that only values above the normal range were considered exclusionary. A post-treatment measurement of coagulation parameters was added to ensure the subject's safety upon completing the trial. Based on the pharmacokinetic (PK) interim analysis low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol measurements were added and the PK sampling scheme for adolescents aged 12-17 years was reduced to harmonize with that already in use for the 18-30 year cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported