Clinical trial results:
A randomized, double-blind, placebo-controlled, flexible dose study to evaluate efficacy and safety of Pramipexole IR (0.0625-0.5 mg/day) versus placebo for 6 weeks in children and adolescents (age 6-17 inclusive) diagnosed with Tourette Disorder according to DSM-IV criteria

Summary

EudraCT number	2008-004460-39
Trial protocol	DE Outside EU/EEA
Global end of trial date	23 June 2009

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	17 May 2015

Trial information

Trial identification

Sponsor protocol code	248.644

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00558467
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein , Germany, 55216
Public contact	Boehringer Ingelheim Pharma GmbH & Co KG, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Pharma GmbH & Co KG, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000041-PIP01-07
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	27 July 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the safety and efficacy of the non ergot dopamine agonist pramipexole for the treatment of tics in children and adolescents (age 6-17 years inclusive) diagnosed with Tourette Disorder according to DSM-IV criteria.
The primary efficacy measure will be the Total Tic Score (TTS) of the YGTSS at 6 weeks.

Protection of trial subjects:

Only subjects who were considered eligible by investigators based on the protocol-specified inclusion and exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2008
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	Germany: 8
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	68
EEA total number of subjects	8

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)	32
Adolescents (12-17 years)	36
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

All study medication was double-blind, so that the treatments were indistinguishable. The Clinical Monitor, the Investigator and the patient were not aware of which treatment group the patient was randomised.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pramipexole

Arm description:

Pramipexole (tablets of 0.0625 mg, 0.125 mg and 0.25 mg) was administered orally. Starting dose 0.0625 mg bid (twice daily), with possible down titration after one week to 0.0625 mg qd (once daily) or optional up titration to 0.125 mg bid, after the second week optional up titration to 0.125 mg tid (three times daily), after the third week optional up titration to 0.25 mg bid.

Arm type	Experimental
Investigational medicinal product name	Sifrol®, Mirapex®, Mirapexin®, Pexola®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pramipexole (tablets of 0.0625 mg, 0.125 mg and 0.25 mg) was orally administered having duration of 6 weeks. Starting dose 0.0625 mg bid, after 7 days patient who tolerated dose 0.0625 mg bid were permitted to up titrate to a dose 0.125 mg bid and increase the dose subsequently. Patients who did not tolerate were permitted to down titrate to a dose of 0.0625 mg qd and continue on this dose for the remainder of the trial.

Arm title	Placebo

Arm description:

Placebo tablets matching the Pramipexole tablets was administered orally.

Arm type	Placebo
Investigational medicinal product name	Placebo matching the Pramipexole tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo (tablets of 0.0625 mg, 0.125 mg and 0.25 mg) to be orally administered having duration of 6 weeks. Starting dose of 0.0625 mg bid matching placebo , after 7 days patient who

tolerated dose 0.0625mg bid were permitted to up titrate to a dose 0.125 mg bid matcing placebo and increase the dose subsequently. Patients who did not tolerate were permitted to down titrate to a dose of 0.0625 mg qd matching placebo and continue on this dose for the remainder of the trial.

Number of subjects in period 1[1]	Pramipexole	Placebo
Started	43	20
Completed	39	19
Not completed	4	1
Adverse event, non-fatal	2	1
Other	1	-
Lack of efficacy	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Pramipexole
Reporting group description:	
Pramipexole (tablets of 0.0625 mg, 0.125 mg and 0.25 mg) was administered orally. Starting dose 0.0625 mg bid (twice daily), with possible down titration after one week to 0.0625 mg qd (once daily) or optional up titration to 0.125 mg bid, after the second week optional up titration to 0.125 mg tid (three times daily), after the third week optional up titration to 0.25 mg bid.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets matching the Pramipexole tablets was administered orally.	

Reporting group values	Pramipexole	Placebo	Total
Number of subjects	43	20	63
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	12.2	11.1	
standard deviation	± 2.4	± 3.2	-
Gender categorical Units: Subjects			
Female	8	2	10
Male	35	18	53
Attention Deficit Hyperactive Disorder			
Diagnosis of disorder was performed using National Institute of Mental Health Diagnostic Interview Schedule for Children (NIMH DISC IV) and resulted in patients being classified as negative diagnosis, intermediate diagnosis and positive diagnosis for disorder.			
Units: Subjects			
Intermediate	6	3	9
Negative	22	9	31
Positive	15	8	23
Duration of Tourettes syndrome Units: Subjects			
1-5 years	19	10	29
Less than 1 year	12	6	18
More than 5 years	12	4	16
Ethnicity, Customized Units: Subjects			
Hispanic/Latino	5	2	7
Not Hispanic/Latino	38	18	56
Obsessive Compulsive Disorder			
Diagnosis of disorder was performed using National Institute of Mental Health Diagnostic Interview Schedule for Children (NIMH DISC IV) and resulted in patients being classified as negative, intermediate and positive for disorder.			
Units: Subjects			
Intermediate	3	1	4
Negative	37	16	53
Positive	3	3	6

Race, Customized Units: Subjects			
Black/African American	4	2	6
White	39	18	57
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	22.575	20.085	
standard deviation	± 5.656	± 5.324	-
Height Units: Centimeters			
arithmetic mean	155.3	150.7	
standard deviation	± 16.2	± 21.6	-
Weight Units: kilogram(s)			
arithmetic mean	55.87	47.48	
standard deviation	± 20.64	± 21.29	-

End points

End points reporting groups

Reporting group title	Pramipexole
Reporting group description:	
Pramipexole (tablets of 0.0625 mg, 0.125 mg and 0.25 mg) was administered orally. Starting dose 0.0625 mg bid (twice daily), with possible down titration after one week to 0.0625 mg qd (once daily) or optional up titration to 0.125 mg bid, after the second week optional up titration to 0.125 mg tid (three times daily), after the third week optional up titration to 0.25 mg bid.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets matching the Pramipexole tablets was administered orally.	

Primary: Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale after 6 weeks of treatment

End point title	Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale after 6 weeks of treatment
End point description:	
Total Tic Score is the sum of ten individual ratings of the impairment due to tics. Each scale ranges from 0 (None/Absent) to 5 (Severe) and total score ranges from 0 to 50. Analysis was adjusted for baseline total tic score and age as linear covariates. The Full Analysis Set (FAS) included all patients who were randomised and have both a baseline and at least one post-baseline TTS value. This data set, used for the primary analysis for the primary endpoint, included 62 patients.	
End point type	Primary
End point timeframe:	
baseline and week 6	

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[1]	20[2]		
Units: score on a scale				
least squares mean (standard error)	-7.16 (± 1.38)	-7.17 (± 2.02)		

Notes:

[1] - FAS Set

[2] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo
Statistical analysis description:	
The analysis of covariance (ANCOVA) model with treatment and pooled center fixed classification effects and the baseline TTS score and age as linear covariates was used for comparing treatment effects on Mean change from baseline to end of treatment visit in Total Tic Score (TTS) of the Yale Global Tic Severity Scale. The Last Observation Carried Forward (LOCF) method was used to handle missing data. Least square mean difference to placebo is calculated.	
Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996
Method	ANCOVA
Parameter estimate	Least Squares mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.95
upper limit	4.97

Secondary: Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 1

End point title	Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 1

End point description:

Total Tic Score is the sum of ten individual ratings of the impairment due to tics. Each scale ranges from 0 (None/Absent) to 5 (Severe) and total score ranges from 0 to 50

End point type	Secondary

End point timeframe:

baseline and week 1

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[3]	20[4]		
Units: score on a scale				
arithmetic mean (standard deviation)	-4.1 (± 5.4)	-3.7 (± 4.1)		

Notes:

[3] - FAS Set

[4] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Analysis comparing treatment effects on Mean change from baseline to end of treatment visit in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 1.

The least square mean differences to placebo group was calculated.

Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
Method	Repeated Measures
Parameter estimate	Least square means difference
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.81
upper limit	-2.08
Variability estimate	Standard error of the mean
Dispersion value	0.95

Secondary: Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 2

End point title	Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 2

End point description:

Total Tic Score is the sum of ten individual ratings of the impairment due to tics. Each scale ranges from 0 (None/Absent) to 5 (Severe) and total score ranges from 0 to 50

End point type	Secondary

End point timeframe:

baseline and week 2

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[5]	19[6]		
Units: score on a scale				
arithmetic mean (standard deviation)	-5 (± 7.4)	-5.3 (± 7.9)		

Notes:

[5] - FAS Set
41 patients data were available for this enpoint, so 41 patients were analysed.
[6] - FAS Set
19 patients data were available for this enpoint, so 19 patients were analysed.

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Analysis comparing treatment effects on Mean change from baseline to end of treatment visit in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 2.

The least square mean differences to placebo group was calculated.

Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
Method	Repeated measures
Parameter estimate	Least square means difference
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.21
upper limit	-3.39
Variability estimate	Standard error of the mean
Dispersion value	0.97

Secondary: Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 3

End point title	Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 3

End point description:

Total Tic Score is the sum of ten individual ratings of the impairment due to tics. Each scale ranges from 0 (None/Absent) to 5 (Severe) and total score ranges from 0 to 50

End point type	Secondary

End point timeframe:

baseline and week 3

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[7]	19[8]		
Units: score on a scale				
arithmetic mean (standard deviation)	-5.4 (± 6.3)	-6.2 (± 6.3)		

Notes:

[7] - FAS Set
41 patients data were available for this enpoint, so 41 patients were analysed.
[8] - FAS Set
19 patients data were available for this enpoint, so 19 patients were analysed.

Statistical analyses

Statistical analysis title	Placebo Vs Pramipexole

Statistical analysis description:

Analysis comparing treatment effects on Mean change from baseline to end of treatment visit in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 3.

The least square mean differences to placebo group was calculated.

Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
Method	Repeated Measures
Parameter estimate	Least square means difference
Point estimate	-5.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.88
upper limit	-4.06
Variability estimate	Standard error of the mean
Dispersion value	0.97

Secondary: Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 4

End point title	Mean change from baseline in Total Tic Score of the Yale Global Tic Severity Scale at week 4

End point description:

Total Tic Score is the sum of ten individual ratings of the impairment due to tics. Each scale ranges from 0 (None/Absent) to 5 (Severe) and total score ranges from 0 to 50

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[9]	19[10]		
Units: score on a scale				
arithmetic mean (standard deviation)	-6.4 (± 7.3)	-6 (± 7.9)		

Notes:

[9] - FAS Set
40 patients data were available for this enpoint, so 40 patients were analysed.
[10] - FAS Set
19 patients data were available for this enpoint, so 19 patients were analysed .

Statistical analyses

Statistical analysis title	Placebo Vs Pramipexole

Statistical analysis description:

This Repeated measure mixed effect model included effects accounting for the following sources of variation: “treatment” and ”center” as fixed effects, “time” as repeated effect, the interaction effect ”treatment-by time” and the respective baseline as covariates. The covariance structure was ”Compound symmetry”.

The least square mean differences to placebo group was calculated.

Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
Method	Repeated measures
Parameter estimate	Least square means difference
Point estimate	-6.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.31
upper limit	-4.47
Variability estimate	Standard error of the mean
Dispersion value	0.97

Secondary: Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 6

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 6

End point description:

Total Score is a rating of the overall impairment due to motor and phonic tics. The scale ranges from 0 (None) to 50 (Severe)

End point type	Secondary

End point timeframe:

baseline and week 6

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[11]	20[12]		
Units: score on a scale				
arithmetic mean (standard deviation)	-16.7 (± 16.8)	-15.8 (± 24.2)		

Notes:

[11] - FAS Set

[12] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

The analysis of covariance (ANCOVA) model with treatment and pooled center fixed classification effects and the baseline Total score and age as linear covariates was used for comparing treatment effects on Mean change from baseline to end of treatment visit in Total Score of the Yale Global Tic
Severity Scale due to motor and phonic tics at week 6. The Last Observation Carried Forward (LOCF) method was used to handle missing data.
Least square mean difference to placebo is calculated.

Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.978
Method	ANCOVA
Parameter estimate	Least Squares Mean differnce
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.05
upper limit	10.75

Secondary: Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 1

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 1

End point description:

Total Score is a rating of the overall impairment due to motor and phonic tics. The scale ranges from 0 (None) to 50 (Severe)

End point type	Secondary

End point timeframe:

baseline and week 1

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[13]	20[14]		
Units: score on a scale				
arithmetic mean (standard deviation)	-8.8 (± 11.1)	-6.2 (± 13.3)		

Notes:

[13] - FAS Set

[14] - FAS Set

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 2

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 2

End point description:

Total Score is a rating of the overall impairment due to motor and phonic tics. The scale ranges from 0 (None) to 50 (Severe)

End point type	Secondary

End point timeframe:

baseline and week 2

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[15]	19[16]		
Units: score on a scale				
arithmetic mean (standard deviation)	-10.6 (± 17.5)	-9.5 (± 16.1)		

Notes:

[15] - FAS Set
41 patients data were available for this enpoint, so 41 patients were analysed.
[16] - FAS Set
19 patients data were available for this enpoint, so 19 patients were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 3

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 3

End point description:

Total Score is a rating of the overall impairment due to motor and phonic tics. The scale ranges from 0 (None) to 50 (Severe)

End point type	Secondary

End point timeframe:

baseline and week 3

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[17]	19[18]		
Units: score on a scale				
arithmetic mean (standard deviation)	-12.2 (± 15.7)	-14.1 (± 17.2)		

Notes:

[17] - FAS Set
41 patients data were available for this enpoint, so 41 patients were analysed.
[18] - FAS Set
19 patients data were available for this enpoint, so 19 patients were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 4

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale due to motor and phonic tics at week 4

End point description:

Total Score is a rating of the overall impairment due to motor and phonic tics. The scale ranges from 0 (None) to 50 (Severe)

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[19]	19[20]		
Units: score on a scale				
arithmetic mean (standard deviation)	-13.9 (± 15.7)	-15.5 (± 18.2)		

Notes:

[19] - FAS Set
40 patients data were available for this enpoint, so 40 patients were analysed.
[20] - FAS Set
19 patients data were available for this enpoint, so 19 patients were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 1

End point title	Clinical Global Impressions - Improvement at week 1

End point description:

Overall improvement during the last week compared to baseline ranging from 1 (very much improved), 2 (much improved), to 7 (very much worse). Responder has 'very much' or 'much' improvement. Non responder has less improvement than 'much' improvement.

End point type	Secondary

End point timeframe:

baseline and week 1

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[21]	20[22]		
Units: Number of Patients				
Responder	5	0		
Not Responder	37	20		

Notes:

[21] - FAS Set

[22] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1052
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Improvement at week 2

End point title	Clinical Global Impressions - Improvement at week 2

End point description:

Overall improvement during the last week compared to baseline ranging from 1 (very much improved), 2 (much improved), to 7 (very much worse). Responder has 'very much' or 'much' improvement. Non responder has less improvement than 'much' improvement.

End point type	Secondary

End point timeframe:

baseline and week 2

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[23]	20[24]		
Units: Number of Patients				
Responder	6	1		
Not Responder	36	19		

Notes:

[23] - FAS Set

[24] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2274
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Improvement at week 3

End point title	Clinical Global Impressions - Improvement at week 3

End point description:

Overall improvement during the last week compared to baseline ranging from 1 (very much improved), 2 (much improved), to 7 (very much worse). Responder has 'very much' or 'much' improvement. Non

responder has less improvement than 'much' improvement.

End point type	Secondary

End point timeframe:

baseline and week 3

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[25]	20[26]		
Units: Number of Patients				
Responder	5	2		
Not Responder	37	18		

Notes:

[25] - FAS Set

[26] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7691
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Improvement at week 4

End point title	Clinical Global Impressions - Improvement at week 4

End point description:

Overall improvement during the last week compared to baseline ranging from 1 (very much improved), 2 (much improved), to 7 (very much worse). Responder has 'very much' or 'much' improvement. Non responder has less improvement than 'much' improvement.

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[27]	20[28]		
Units: Number of Patients				
Responder	6	7		
Not Responder	36	13		

Notes:

[27] - FAS Set

[28] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Palcebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0674
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Improvement at week 6

End point title	Clinical Global Impressions - Improvement at week 6

End point description:

Overall improvement during the last week compared to baseline ranging from 1 (very much improved), 2 (much improved), to 7 (very much worse). Responder has 'very much' or 'much' improvement. Non responder has less improvement than 'much' improvement.

End point type	Secondary

End point timeframe:

baseline and week 6

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[29]	20[30]		
Units: Number of Patients				
Responder	11	7		
Not Responder	31	13		

Notes:

[29] - FAS Set

[30] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4944
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Severity of Illness at week 1

End point title	Clinical Global Impressions - Severity of Illness at week 1

End point description:

Assessment of the overall severity of illness on a scale ranging from 1 (not at all ill) to 7 (the most extremely ill patients). Improved, Unchanged and Worsened responses correspond to changes from baseline of: -2 or less, -1 to +1, and 2 or greater.

End point type	Secondary

End point timeframe:

baseline and week 1

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[31]	20[32]		
Units: Number of Patients				
Improved	4	0		
Unchanged	38	20		
Worsened	0	0		

Notes:

[31] - FAS Set

[32] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Severity of Illness at week 2

End point title	Clinical Global Impressions - Severity of Illness at week 2

End point description:

Assessment of the overall severity of illness on a scale ranging from 1 (not at all ill) to 7 (the most extremely ill patients). Improved, Unchanged and Worsened responses correspond to changes from baseline of: -2 or less, -1 to +1, and 2 or greater.

End point type	Secondary

End point timeframe:

baseline and week 2

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[33]	20[34]		
Units: Number of Patients				
Improved	4	1		
Unchanged	37	19		
Worsened	1	0		

Notes:

[33] - FAS Set

[34] - FAS Set

Statistical analyses

Statistical analysis title	Placebo Vs Pramipexole

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6375
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Severity of Illness at week 3

End point title	Clinical Global Impressions - Severity of Illness at week 3

End point description:

Assessment of the overall severity of illness on a scale ranging from 1 (not at all ill) to 7 (the most extremely ill patients). Improved, Unchanged and Worsened responses correspond to changes from baseline of: -2 or less, -1 to +1, and 2 or greater.

End point type	Secondary

End point timeframe:

baseline and week 3

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[35]	20[36]		
Units: Number of Patients				
Improved	4	3		
Unchanged	37	17		
Worsened	1	0		

Notes:

[35] - FAS Set

[36] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Placebo v Pramipexole
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6625
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Severity of Illness at week 4

End point title	Clinical Global Impressions - Severity of Illness at week 4

End point description:

Assessment of the overall severity of illness on a scale ranging from 1 (not at all ill) to 7 (the most extremely ill patients). Improved, Unchanged and Worsened responses correspond to changes from baseline of: -2 or less, -1 to +1, and 2 or greater.

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[37]	20[38]		
Units: Number of Patients				
Improved	4	4		
Unchanged	38	16		
Worsened	0	0		

Notes:
[37] - FAS Set
[38] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Placebo v Pramipexole
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2664
Method	Cochran-Mantel-Haenszel

Secondary: Clinical Global Impressions - Severity of Illness at week 6

End point title	Clinical Global Impressions - Severity of Illness at week 6

End point description:

Assessment of the overall severity of illness on a scale ranging from 1 (not at all ill) to 7 (the most extremely ill patients). Improved, Unchanged and Worsened responses correspond to changes from baseline of: -2 or less, -1 to +1, and 2 or greater.

End point type	Secondary

End point timeframe:

baseline and week 6

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[39]	20[40]		
Units: Number of Patients				
Improved	10	4		
Unchanged	32	16		
Worsened	0	0		

Notes:
[39] - FAS Set
[40] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7302
Method	Cochran-Mantel-Haenszel

Secondary: Patient Global Impression response at week 1

End point title	Patient Global Impression response at week 1

End point description:

Assessment of the change of the patient's overall condition during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much better) to 7 (very much worse). A responder is defined as having a response of very much (1) or much better (2).

End point type	Secondary

End point timeframe:

baseline and week 1

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[41]	20[42]		
Units: Number of Patients				
Responder	7	4		
Not Responder	35	16		

Notes:

[41] - FAS Set

[42] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Placebo v Pramipexole
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7723
Method	Cochran-Mantel-Haenszel

Secondary: Patient Global Impression response at week 2

End point title	Patient Global Impression response at week 2

End point description:

Assessment of the change of the patient's overall condition during the last week compared to the

patient's condition at baseline on a scale ranging from 1 (very much better) to 7 (very much worse). A responder is defined as having a response of very much (1) or much better (2).

End point type	Secondary

End point timeframe:

baseline and week 2

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[43]	20[44]		
Units: Number of Patients				
Responder	9	6		
Not Responder	33	14		

Notes:

[43] - FAS Set

[44] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4852
Method	Cochran-Mantel-Haenszel

Secondary: Patient Global Impression response at week 3

End point title	Patient Global Impression response at week 3

End point description:

Assessment of the change of the patient's overall condition during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much better) to 7 (very much worse). A responder is defined as having a response of very much (1) or much better (2).

End point type	Secondary

End point timeframe:

baseline and week 3

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[45]	20[46]		
Units: Number of Patients				
Responder	7	5		
Not Responder	35	15		

Notes:

[45] - FAS Set

[46] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Placebo v Pramipexole
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4607
Method	Cochran-Mantel-Haenszel

Secondary: Patient Global Impression response at week 4

End point title	Patient Global Impression response at week 4

End point description:

Assessment of the change of the patient's overall condition during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much better) to 7 (very much worse). A responder is defined as having a response of very much (1) or much better (2).

End point type	Secondary

End point timeframe:

baseline and week 4

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[47]	20[48]		
Units: Number of Patients				
Responder	7	4		
Not Responder	35	16		

Notes:

[47] - FAS Set

[48] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7723
Method	Cochran-Mantel-Haenszel

Secondary: Patient Global Impression response at week 6

End point title	Patient Global Impression response at week 6

End point description:

Assessment of the change of the patient's overall condition during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much better) to 7 (very much worse). A responder is defined as having a response of very much (1) or much better (2).

End point type	Secondary

End point timeframe:

baseline and week 6

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[49]	20[50]		
Units: Number of Patients				
Responder	12	6		
Not Responder	30	14		

Notes:

[49] - FAS Set

[50] - FAS Set

Statistical analyses

Statistical analysis title	Pramipexole vs Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test with age group (6-9, 10-13, 14-17 years) stratification was performed. The Last Observation Carried Forward (LOCF) method was used to handle missing data.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9389
Method	Cochran-Mantel-Haenszel

Secondary: Clinically Significant Abnormalities

End point title	Clinically Significant Abnormalities

End point description:

Clinical significant abnormalities in vital signs (blood pressure, orthostatic reaction and pulse rate), height, weight, Tanner Staging, ECG, laboratory parameters, blood hematology and electrolyte assessments, serum chemistry and urine analyses.

The Treated Set (TS) included all patients who were randomised, dispensed study medication and were documented to have taken at least one dose of study medication.

End point type	Secondary

End point timeframe:

baseline and week 6

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[51]	19[52]		
Units: participants				
Phosphate - increase	5	2		
Bilirubin, total - increase	1	0		
Tachycardia	1	0		
Orthostatic hypotension	4	1		

Notes:

[51] - FAS Set
40 patients data were available, so 40 patients were analysed for this enpoint.
[52] - FAS Set
19 patients data were available, so 19 patients were analysed for this enpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All events with an onset after the first dose of study medication and up to a period of 48 hours after the last dose of study medication were assigned to the treatment period, upto 52 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Pramipexole

Reporting group description:

Pramipexole (tablets of 0.0625 mg, 0.125 mg and 0.25 mg) was administered orally. Starting dose 0.0625 mg bid, with possible down titration after one week to 0.0625 mg qd or optional up titration to 0.125 mg bid, after the second week optional up titration to 0.125 mg tid, after the third week optional up titration to 0.25 mg bid.

Reporting group title	Placebo

Reporting group description:

Placebo tablets matching the Pramipexole tablets was administered orally.

Serious adverse events	Pramipexole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 43 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 43 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pramipexole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 43 (58.14%)	13 / 20 (65.00%)	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	4 / 43 (9.30%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 43 (27.91%)	5 / 20 (25.00%)	
occurrences (all)	26	7	
Dizziness			
subjects affected / exposed	3 / 43 (6.98%)	3 / 20 (15.00%)	
occurrences (all)	5	3	
Somnolence			
subjects affected / exposed	3 / 43 (6.98%)	1 / 20 (5.00%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 43 (9.30%)	2 / 20 (10.00%)	
occurrences (all)	6	2	
Pyrexia			
subjects affected / exposed	2 / 43 (4.65%)	2 / 20 (10.00%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 43 (18.60%)	2 / 20 (10.00%)	
occurrences (all)	10	2	
Vomiting			
subjects affected / exposed	5 / 43 (11.63%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Diarrhoea			
subjects affected / exposed	3 / 43 (6.98%)	2 / 20 (10.00%)	
occurrences (all)	3	4	
Abdominal pain upper			
subjects affected / exposed	3 / 43 (6.98%)	1 / 20 (5.00%)	
occurrences (all)	5	1	

Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 43 (6.98%)	3 / 20 (15.00%)	
occurrences (all)	3	3	
Cough			
subjects affected / exposed	3 / 43 (6.98%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Dyspnoea			
subjects affected / exposed	3 / 43 (6.98%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Tic			
subjects affected / exposed	1 / 43 (2.33%)	2 / 20 (10.00%)	
occurrences (all)	1	4	
Sleep disorder			
subjects affected / exposed	3 / 43 (6.98%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	4 / 43 (9.30%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 43 (4.65%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Upper respiratory tract infection			
subjects affected / exposed	3 / 43 (6.98%)	1 / 20 (5.00%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2007	• Provided a revised means to assess IQ of potential patients for entry into the study, updated the inclusion criteria accordingly. • Provided more specific instructions on the down titration process at the end of the treatment phase with study medication. • Expanded the list of restricted concomitant medications.
06 August 2008	• The trial duration was extended and centers in Germany were added in order to achieve full recruitment of planned sample size. • In order to optimize patient safety monitoring a Data Monitoring Committee was added and Visit 8 was required as a clinic visit for all patients. • Inclusion/exclusion criteria were modified. • Requirements, processes and other protocol activities were clarified: concomitant medications; dosing time; medication dispensing; PK samples; eye examination; YGTSS and CY-BOCS administration. • Logistical and/or administrative data were corrected: addition of EudraCT Number and trade name for pramipexole; change in personnel; total number of potential daily doses; typographical error on Day of Visit 8; logistical information for the trial medication supply; K-BIT2 for non-English speaking patients; Lab parameters; references.
15 April 2009	• Trial duration was extended due to an increase in sample size. • The number of study sites was revised to more accurately reflect the actual number of sites participating in the study. • Sample size was increased, as per the FDA's Written Request to increase the power of the study to 85%. • Height was added as a safety parameter. • Inconsistencies in the protocol were corrected, and a clarification to the protocol was made. • Ethnicity was added to patient demographics to comply with FDA's Written Request. • The restriction on the maximum number of patients enrolled per site was removed to improve patient recruitment. • Tanner Staging was added as an additional safety measure to be evaluated by the DMC. • Reference citations were added to the reference list.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported