Clinical trial results:
An open-label, flexible dose, follow-up study to evaluate safety and efficacy of oral pramipexole (0.0625-0.5 mg/day) for 24 weeks in children and adolescents (age 6-17 years) diagnosed with Tourette Syndrome according to DSM-IV criteria and who have completed the double-blind phase of either study 248.641 or 248.644.

Summary

EudraCT number	2008-000342-32
Trial protocol	DE Outside EU/EEA
Global end of trial date	15 October 2009

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	248.642

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00681863
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, 55216 Ingelheim am Rhein, Germany,
Public contact	Boehringer Ingelheim Pharma GmbH & Co KG, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Pharma GmbH & Co KG, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , +1 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this open-label, flexible dose study is to assess the safety and efficacy of pramipexole over a 24-week period in children and adolescents (age 6-17 years inclusive) diagnosed with Tourette Syndrome according to DSM-IV criteria and who have completed either Study 248.641 or 248.644.
The safety of pramipexole will be evaluated collectively for the incidence of adverse events, the proportion of withdrawals due to drug related adverse events, and the assessment of the following scales:
• Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS);
• Child Behavior Checklist (CBCL) ;
• DuPaul Attention-Deficit / Hyperactivity Disorder (ADHD) Rating Scale-IV;
• Child Depression Inventory-Short Version CDI-S;
• Multidimensional Anxiety Scale for Children (MASC).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 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: 2
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	46
EEA total number of subjects	2

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)	21
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

46 participants were enrolled in the trial. Out of these enrolled participants, 1 participant did not enter the trial.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that the subject met all strictly implemented inclusion/exclusion criteria. Patients with Tourette Syndrome who have completed the preceding Study 248.641 or 248.644 were assessed for entry into this rollover study.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pramipexole

Arm description:

4 weeks individual dose titration starting with 0.0625 mg BID (twice daily), down-titration to 0.0625 QD (once daily) if not tolerated, and next steps 0.125 mg BID, 0.125 mg TID (three times daily) and 0.25 mg BID, according to efficacy assessment; established optimal dose for the remainder of the 24-week treatment period.

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

Dosage and administration details:

4 weeks individual dose titration starting with 0.0625 mg BID (twice daily), down-titration to 0.0625 QD (once daily) if not tolerated, and next steps 0.125 mg BID, 0.125 mg TID (three times daily) and 0.25 mg BID, according to efficacy assessment; established optimal dose for the remainder of the 24-week treatment period.

Number of subjects in period 1	Pramipexole
Started	45
Completed	22
Not completed	23
Adverse event, non-fatal	1
'Reason other than those specified '	18
Lost to follow-up	2
Lack of efficacy	2

Baseline characteristics

Reporting groups[1]	
Reporting group title	Pramipexole
Reporting group description:	
4 weeks individual dose titration starting with 0.0625 mg BID (twice daily), down-titration to 0.0625 QD (once daily) if not tolerated, and next steps 0.125 mg BID, 0.125 mg TID (three times daily) and 0.25 mg BID, according to efficacy assessment; established optimal dose for the remainder of the 24-week treatment period.	

Notes:

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

Reporting group values	Pramipexole	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Age Continuous | Units: Years arithmetic mean standard deviation	 11.8 ± 2.8	 -	
Gender, Male/Female Units: Participants			
Female	9	9	
Male	36	36	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	6	
Not Hispanic or Latino	38	38	
Unknown or Not Reported	1	1	
Race/Ethnicity, Customized Units: Subjects			
Black or African American	5	5	
White	40	40	
Study Specific Characteristic			
Obsessive Compulsive Disorder			
Units: Subjects			
Positive	4	4	
Intermediate	4	4	
Negative	37	37	
Study Specific Characteristic			
Attention Deficit Hyperactive Disorder			
Units: Subjects			
Positive	17	17	
Intermediate	6	6	
Negative	22	22	
Study Specific Characteristic			
Treatment received in previous trial (NCT00558467)			
Units: Subjects			

Received placebo	14	14	
Received pramipexole	31	31	
Duration of Tourettes Syndrome			
Duration of Tourettes Syndrome			
Units: Subjects			
Less than 1 year	15	15	
1 to 5 years	20	20	
More than 5 years	10	10	
Study Specific Characteristic |			
Height			
Units: centimeters			
arithmetic mean	152.6		
standard deviation	± 19.4	-	
Study Specific Characteristic |			
Weight			
Units: kilograms			
arithmetic mean	53.01		
standard deviation	± 21.58	-	
Study Specific Characteristic |			
Body mass index			
Units: kilograms/square meter			
arithmetic mean	22.064		
standard deviation	± 5.93	-	
Study Specific Characteristic |			
Body temperature			
Units: Degrees centigrade			
arithmetic mean	36.752		
standard deviation	± 0.718	-	
Study Specific Characteristic |			
Respiration			
Units: breaths/minute			
arithmetic mean	17.4		
standard deviation	± 2	-	

End points

End points reporting groups

Reporting group title	Pramipexole

Reporting group description:

4 weeks individual dose titration starting with 0.0625 mg BID (twice daily), down-titration to 0.0625 QD (once daily) if not tolerated, and next steps 0.125 mg BID, 0.125 mg TID (three times daily) and 0.25 mg BID, according to efficacy assessment; established optimal dose for the remainder of the 24-week treatment period.

Primary: Patients with Adverse Events leading to discontinuation of trial drug

End point title	Patients with Adverse Events leading to discontinuation of trial drug[1]

End point description:

Number of patients with Adverse Events leading to discontinuation of trial drug.

The Treated Set (TS) included all patients who were entered, dispensed study medication and were documented to have taken at least one dose of study medication. This data set, used to summarise the safety results, included all 45 patients that were entered in this trial.

End point type	Primary

End point timeframe:

24 Weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	45[2]			
Units: participants	1			

Notes:

[2] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at End of treatment visit

End point title	Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at End of treatment visit

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.

The Full Analysis Set (FAS) included all patients who were included in the treated set and have both a baseline and at least one post-treatment TTS value. This data set, used to summarise the efficacy results, included all 45 patients that were entered and treated in this trial.

End point type	Secondary

End point timeframe:

baseline and End of treatment visit (week 24)

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	45[3]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-9.8 (± 8.9)			

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at the end of treatment visit

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at the end of treatment visit

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 end of treatment visit

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	45[4]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-22 (± 21)			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from baseline in Total Tic Score (TTS) 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			
Subject group type	Reporting group			
Number of subjects analysed	45[5]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-7.2 (± 8.5)			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from baseline in Total Tic Score (TTS) 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			
Subject group type	Reporting group			
Number of subjects analysed	45[6]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-8.3 (± 7.7)			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from baseline in Total Tic Score (TTS) 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			
Subject group type	Reporting group			
Number of subjects analysed	44[7]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-8.6 (± 8.6)			

Notes:

[7] - FAS(Only patients with baseline and week 3 values were analysed)

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from baseline in Total Tic Score (TTS) 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			
Subject group type	Reporting group			
Number of subjects analysed	44[8]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-9.3 (± 9.7)			

Notes:

[8] - FAS (Only patients with baseline and week 4 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 8

End point title	Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 8

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 8

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	41[9]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-10.7 (± 9.4)			

Notes:

[9] - FAS (Only patients with baseline and week 8 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 12

End point title	Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 12

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 12

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	35[10]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-12.3 (± 9)			

Notes:

[10] - FAS (Only patients with baseline and week 12 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 16

End point title	Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 16

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 16

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	32[11]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-12.4 (± 9.3)			

Notes:

[11] - FAS (Only patients with baseline and week 16 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 20

End point title	Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 20

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 20

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	26[12]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-11.7 (± 11.3)			

Notes:

[12] - FAS (Only patients with baseline and week 20 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 24

End point title	Mean change from baseline in Total Tic Score (TTS) of the Yale Global Tic Severity Scale at week 24

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 24

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	22[13]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-9.3 (± 10.4)			

Notes:

[13] - FAS (Only patients with baseline and week 24 values 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 at week 1

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale 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			
Subject group type	Reporting group			
Number of subjects analysed	45[14]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-14.5 (± 18.2)			

Notes:

[14] - FAS

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale 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			
Subject group type	Reporting group			
Number of subjects analysed	45[15]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-17.4 (± 17.6)			

Notes:

[15] - FAS

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale 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			
Subject group type	Reporting group			
Number of subjects analysed	44[16]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-18.4 (± 19.8)			

Notes:

[16] - FAS (Only patients with baseline and week 3 values 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 at week 4

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale 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			
Subject group type	Reporting group			
Number of subjects analysed	44[17]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-20.9 (± 21.5)			

Notes:

[17] - FAS (Only patients with baseline and week 4 values 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 at week 8

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at week 8

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 8

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	41[18]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-22.4 (± 21.9)			

Notes:

[18] - FAS (Only patients with baseline and week 8 values 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 at week 12

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at week 12

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 12

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	35[19]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-27.7 (± 20.9)			

Notes:

[19] - FAS (Only patients with baseline and week 12 values 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 at week 16

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at week 16

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 16

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	32[20]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-28.3 (± 20.2)			

Notes:

[20] - FAS (Only patients with baseline and week 16 values 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 at week 20

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at week 20

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 20

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	26[21]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-26.7 (± 24.9)			

Notes:

[21] - FAS (Only patients with baseline and week 20 values 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 at week 24

End point title	Mean change from baseline in Total Score of the Yale Global Tic Severity Scale at week 24

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 24

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	22[22]			
Units: Score on a scale				
arithmetic mean (standard deviation)	-22 (± 23.6)			

Notes:

[22] - FAS (Only patients with baseline and week 24 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Severity of Illness, Categorized at week 24

End point title	Clinical Global Impressions - Severity of Illness, Categorized at week 24

End point description:

Assessment of the overall severity of illness on a scale ranging from 1 (not at all ill) to 7 (among the most extremely ill patients). 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:

week 24

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	42[23]			
Units: participants				
Improved (change score <= -2)	11			
Unchanged (change score of -1, 0, or +1)	31			
Worsened (change score >= +2)	0			

Notes:

[23] - FAS (Only patients with baseline and week 24 values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Severity of Illness at week 24

End point title	Clinical Global Impressions - Severity of Illness at week 24

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:

week 24

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	42[24]			
Units: score on a scale				
arithmetic mean (standard deviation)	-1.1 (± 1.1)			

Notes:

[24] - FAS (Only patients with baseline and week 24 values were analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 2

End point title	Clinical Global Impressions - Improvement at week 2

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 2

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[25]			
Units: participants				

Notes:

[25] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

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:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 1

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[26]			
Units: participants				

Notes:

[26] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 3

End point title	Clinical Global Impressions - Improvement at week 3

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 3

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[27]			
Units: participants				

Notes:

[27] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 4

End point title	Clinical Global Impressions - Improvement at week 4

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 4

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[28]			
Units: participants				

Notes:

[28] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 8

End point title	Clinical Global Impressions - Improvement at week 8

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 8

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[29]			
Units: participants				

Notes:

[29] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 16

End point title	Clinical Global Impressions - Improvement at week 16

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 16

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[30]			
Units: participants				

Notes:

[30] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 12

End point title	Clinical Global Impressions - Improvement at week 12

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 12

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[31]			
Units: participants				

Notes:

[31] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 20

End point title	Clinical Global Impressions - Improvement at week 20

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 20

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[32]			
Units: participants				

Notes:

[32] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Improvement at week 24

End point title	Clinical Global Impressions - Improvement at week 24

End point description:

Assessment of the overall improvement during the last week compared to the patient's condition at baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

week 24

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	45[33]			
Units: participants				
Responder (Much improved or Very much improved)	22			
Not Responder	23			

Notes:

[33] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 1

End point title	Patient Global Impression - Improvement 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:

week 1

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[34]			
Units: participants				

Notes:

[34] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 2

End point title	Patient Global Impression - Improvement 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:

week 2

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[35]			
Units: participants				

Notes:

[35] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 3

End point title	Patient Global Impression - Improvement 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:

week 3

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[36]			
Units: participants				

Notes:

[36] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 4

End point title	Patient Global Impression - Improvement 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:

week 4

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[37]			
Units: participants				

Notes:

[37] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 8

End point title	Patient Global Impression - Improvement at week 8

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:

week 8

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[38]			
Units: participants				

Notes:

[38] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 12

End point title	Patient Global Impression - Improvement at week 12

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:

week 12

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[39]			
Units: participants				

Notes:

[39] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 16

End point title	Patient Global Impression - Improvement at week 16

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:

week 16

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[40]			
Units: participants				

Notes:

[40] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 20

End point title	Patient Global Impression - Improvement at week 20

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:

week 20

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	0[41]			
Units: participants				

Notes:

[41] - Outcome measure was not analyzed due to the premature ending of the trial (0 participants analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression - Improvement at week 24

End point title	Patient Global Impression - Improvement at week 24

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:

week 24

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	45[42]			
Units: participants				
Responder (Much better or Very much better)	17			
Not Responder	28			

Notes:

[42] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients with possible clinically significant abnormalities for laboratory parameters

End point title	Frequency of patients with possible clinically significant abnormalities for laboratory parameters

End point description:

Clinical Relevant Abnormalities for laboratory parameters. Any new or clinically relevant worsening of baseline conditions was reported as Adverse Events.

The Treated Set (TS) included all patients who were entered, dispensed study medication and were documented to have taken at least one dose of study medication. This data set, used to summarise the safety results, included all 45 patients that were entered in this trial.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Pramipexole			
Subject group type	Reporting group			
Number of subjects analysed	43[43]			
Units: participants				
Haemoglobin - decrease	2			
Eosinophils - increase	3			
Phosphate - increase	2			
Alkaline phosphatase - increase	1			

Notes:

[43] - TS (observed cases)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to the start date of follow-up period, up to 24 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	Pramipexole
Reporting group description:	
4 weeks individual dose titration starting with 0.0625 mg BID, down-titration to 0.0625 QD if not tolerated, and next steps 0.125 mg BID, 0.125 mg TID and 0.25 mg BID, according to efficacy assessment; established optimal dose for the remainder of the 24-week treatment period.	

Serious adverse events	Pramipexole		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pramipexole		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 45 (62.22%)		
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Vascular disorders			
Orthostatic hypotension			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	13		
Dizziness			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Somnolence			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	6		
Vomiting			

subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	6		
Psychiatric disorders			
Tic			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2008	Extended the follow-up period after the end of treatment to optimize patient safety monitoring • Addition of a phone visit (Visit 12) seven days after Visit 11 • Addition of Visit 13, the final visit, 28 days after Visit 11 • Utilization of a Data Monitoring Committee • Current expected AE list should be obtained from the Investigator Brochure • Decision to send study drug to sites in child resistant bottles, not blisters in the maintenance phase • Clarification of: - timing of the eye examination; - duration of the down-titration phase; - duration and on-study medication supply for down-titration phase; - thyroid function parameters: - age-appropriate range for serum creatinine
05 May 2009	Study medication for the down-titration phase to only be supplied in child-resistant bottles

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 October 2009	This open-label follow-up study (subjects who had completed either Study 248.641 or 248.644 were to enter) was prematurely discontinued by Boehringer Ingelheim due to the negative results in the 248.644 study. Thus, the 248.641 study was never initiated, so only patients from 248.644 were entered into this (248.642) study.	-

Notes:

Limitations and caveats

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

The sponsor cancelled this trial prematurely. Thus, enrollment for 248.642 (NCT00681863) was significantly less than what was planned (120 planned vs. 45 entered). Therefore, the objectives of this study could not be fully assessed.

Notes: