



Clinical trial results:

A randomised, double-blind, placebo controlled trial of pramipexole in addition to mood stabilisers for patients with treatment resistant bipolar depression.

Summary

EudraCT number	2018-002869-18
Trial protocol	GB
Global end of trial date	29 October 2022

Results information

Result version number	v1 (current)
This version publication date	11 August 2024
First version publication date	11 August 2024

Trial information

Trial identification

Sponsor protocol code	RES-17-031
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Additional study identifiers

ISRCTN number	ISRCTN72151939
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Research Ethics Committee: 19/NE/0233, NIHR HTA Funder: 16/154/01

Notes:

Sponsors

Sponsor organisation name	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
Sponsor organisation address	Jubilee Road, Gosforth, United Kingdom, NE3 3XT
Public contact	Prof R. Hamish McAllister-Williams, Newcastle University, +44 0191 208 1370, hamish.mcallister-williams@ncl.ac.uk
Scientific contact	Prof R. Hamish McAllister-Williams, Newcastle University, +44 0191 208 1370, hamish.mcallister-williams@ncl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2022
Global end of trial reached?	Yes
Global end of trial date	29 October 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood stabilising medication, over 12 weeks, in the management of patients with treatment resistant bipolar depression.

Protection of trial subjects:

A DMC was convened to undertake independent review. The purpose of this committee was to monitor safety. At the first meeting, the DMC agreed on its charter of operation and how many times the DMC would meet throughout the course of the study. The trial statistician was partially blinded for DMC meetings (treatment arms coded via Group A and Group B until the results reveal meeting which was held at the end of the trial. The senior statistician was fully blinded throughout in line with the rest of the trial management team.

Background therapy:

n/a

Evidence for comparator:

n/a

Actual start date of recruitment	28 November 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 39
Worldwide total number of subjects	39
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	38
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potentially eligible participants were either approached in person by a member of the clinical team and asked for verbal consent for a member of the trial team to get in touch or were approached via an invitation letter and summary sent by post or email. Participants were recruited between 28/11/2019 and 26/05/2022.

Pre-assignment

Screening details:

Patients were identified from secondary care services using patient clinic lists, databases, and research registers. Clinicians were assisted by Clinical Studies Officers or other staff from the Clinical Research Networks where possible. The trial was also advertised to participants directly via posters, trial website and via postal invitations.

Period 1

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

Blinding implementation details:

Randomisation was carried out using Sealed Envelope (a central, secure, 24-hour web-based system with concealed allocation). Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and staff were blinded. Participants were randomised on a 1:1 basis to receive either pramipexole or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pramipexole

Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm type	Experimental
Investigational medicinal product name	Pramipexole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm title	Placebo
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Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

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

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Number of subjects in period 1	Pramipexole	Placebo
Started	18	21
Completed	18	21

Period 2

Period 2 title	Week 12
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was carried out using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded. Participants were randomised on a 1:1 basis to receive either pramipexole or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pramipexole

Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm type	Experimental
Investigational medicinal product name	Pramipexole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm title	Placebo
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Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

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

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Number of subjects in period 2	Pramipexole	Placebo
Started	18	21
Completed	16	20
Not completed	2	1
Consent withdrawn by subject	2	-
death likely by suicide	-	1

Period 3

Period 3 title	Week 24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was carried out using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded. Participants were randomised on a 1:1 basis to receive either pramipexole or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pramipexole

Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm type	Experimental
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Investigational medicinal product name	Pramipexole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm title	Placebo
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Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

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

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Number of subjects in period 3	Pramipexole	Placebo
Started	16	20
Completed	13	17
Not completed	3	3
Physician decision	-	1
unknown	-	1
Withdrawn (due to early trial closure)	3	1

Period 4

Period 4 title	Week 36
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was carried out using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded. Participants were randomised on a 1:1 basis to receive either pramipexole or placebo.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pramipexole
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Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm type	Experimental
Investigational medicinal product name	Pramipexole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm title	Placebo
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Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

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

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Number of subjects in period 4	Pramipexole	Placebo
Started	13	17
Completed	9	10
Not completed	4	7
Physician decision	1	-
Withdrawn (due to early trial closure)	2	6
Lost to follow-up	1	-
moving out of area	-	1

Period 5

Period 5 title	Week 48
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was carried out using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded. Participants were randomised on a 1:1 basis to receive either pramipexole or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pramipexole

Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm type	Experimental
Investigational medicinal product name	Pramipexole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Arm title	Placebo
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Arm description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

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

Dosage and administration details:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Number of subjects in period 5	Pramipexole	Placebo
Started	9	10
Completed	8	8
Not completed	1	2
Withdrawn (due to early trial closure)	1	2

Baseline characteristics

Reporting groups

Reporting group title	Pramipexole
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Reporting group description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Reporting group title	Placebo
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Reporting group description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Reporting group values	Pramipexole	Placebo	Total
Number of subjects	18	21	39
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	20	38
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous Units: years			
median	49	49	
full range (min-max)	40 to 57	36 to 58	-
Gender categorical Units: Subjects			
Female	8	10	18
Male	10	11	21
QIDS-SR score Units: Subjects			
median	15.5	18	
full range (min-max)	12 to 19	16 to 21	-

[illegible]

Primary: QIDS-SR Score at 12 weeks

End point title	QIDS-SR Score at 12 weeks
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End point description:

To evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood stabilising medication, over 12 weeks, in the management of patients with treatment resistant bipolar depression. This was assessed using the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) scores for patients randomised to pramipexole compared to those randomised to placebo at 12 weeks, covarying for baseline QIDS-SR score.

End point type	Primary
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End point timeframe:

12 weeks

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: Subjects				
median (full range (min-max))	10 (0 to 21)	16.5 (2 to 24)		

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) - 12 weeks
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Statistical analysis description:

This is the primary analysis of the primary outcome measure of the PAX-BD trial, as specified in the protocol. The analysis set is the ITT population. The primary outcome measure is QIDS-SR score after 12 weeks and will be analysed using analysis of covariance (ANCOVA) methods in order to compare the 12 week QIDS-SR scores between the treatment groups while adjusting for QIDS-SR score at the time of randomisation (week 0).

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0865 ^[2]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.445
upper limit	6.324
Variability estimate	Standard error of the mean
Dispersion value	1.664

Notes:

[1] - Analysis of the primary outcome measure of QIDS-SR at week 12 used analysis of covariance (ANCOVA) or related regression methods to examine the difference between the trial arms with adjustment for baseline covariates as far as permitted by the achieved sample size. A two-sided significance level of $p < 0.05$ was used throughout. Unadjusted analysis using the t-test, or related regression or ANCOVA methods adjusting only for trial arm, together with other unadjusted analyses, were also undertaken.

[2] - The hypothesis to be tested is H0: The average QIDS-SR score at 12 weeks are equal for both arms (Pramipexole v Placebo) with adjustment for baseline QIDS-SR score.

Secondary: QIDS-SR score at 24, 36 and 48 weeks

End point title	QIDS-SR score at 24, 36 and 48 weeks
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End point description:

To examine the impact of pramipexole treatment on mood and anxiety symptoms over 48 weeks. This will be assessed using the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR). QIDS-SR was collected at the following timepoints during this study: Baseline, Week 12, Week 24, Week 36 and Week 48. Weeks 24, 36 and 48 are reported within this secondary end point section. Baseline is recorded within the Baseline Characteristics section and the week 12 data within the Primary End Point section. This is to save repetition of the same data.

End point type	Secondary
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End point timeframe:

Between baseline and 48 weeks.

End point values	Pramipexole	Placebo	Pramipexole	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13 ^[3]	17 ^[4]	9 ^[5]	10 ^[6]
Units: Subjects				
median (full range (min-max))	12 (2 to 22)	16.5 (2 to 26)	8.5 (0 to 16)	18 (6 to 27)

Notes:

[3] - at 24 weeks

[4] - at 24 weeks

[5] - at 36 weeks

[6] - at 36 weeks

End point values	Pramipexole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8 ^[7]	8 ^[8]		
Units: Subjects				
median (full range (min-max))	8.5 (1 to 14)	18.5 (7 to 24)		

Notes:

[7] - at 48 weeks

[8] - at 48 weeks

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA) - 24 weeks
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Statistical analysis description:

This is the analysis of the secondary objective to examine the impact of pramipexole treatment on mood and anxiety symptoms over 48 weeks as specified in the protocol. The analysis set is the ITT population. The outcome measure was collected via completion of the QIDS-SR score which was completed weekly up to week 48. It was analysed using analysis of covariance (ANCOVA) methods. This analysis covers the week 24 timepoint.

Comparison groups	Pramipexole v Placebo
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Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority ^[9]
P-value	= 0.488
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.275
upper limit	4.645
Variability estimate	Standard error of the mean
Dispersion value	1.686

Notes:

[9] - This is an ad-hoc analysis timepoint. Week 48 was always planned to be analysed, but due to funder decision to close the study early not many participants had reached this planned timepoint. It was therefore considered reasonable to also analyse/present data from weeks 24 and 36 as more participants reached these timepoints.

Statistical analysis title	Analysis of covariance (ANCOVA) - 36 weeks
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Statistical analysis description:

This is the analysis of the secondary objective to examine the impact of pramipexole treatment on mood and anxiety symptoms over 48 weeks as specified in the protocol. The analysis set is the ITT population. The outcome measure was collected via completion of the QIDS-SR score which was completed weekly up to week 48. It was analysed using analysis of covariance (ANCOVA) methods. This analysis covers the week 36 timepoint.

Comparison groups	Pramipexole v Placebo
Number of subjects included in analysis	19
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.008
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	6.278
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.85
upper limit	10.707
Variability estimate	Standard error of the mean
Dispersion value	2.089

Statistical analysis title	Analysis of covariance (ANCOVA) - 48 weeks
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Statistical analysis description:

This is the analysis of the secondary objective to examine the impact of pramipexole treatment on mood and anxiety symptoms over 48 weeks as specified in the protocol. The analysis set is the ITT population. The outcome measure was collected via completion of the QIDS-SR score which was completed weekly up to week 48. It was analysed using analysis of covariance (ANCOVA) methods. This analysis covers the week 48 timepoint.

Comparison groups	Pramipexole v Placebo
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Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.052
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.478
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	11.002
Variability estimate	Standard error of the mean
Dispersion value	2.557

Notes:

[10] - This is an ad-hoc analysis timepoint. Week 48 was always planned to be analysed, but due to funder decision to close the study early not many participants had reached this planned timepoint. It was therefore considered reasonable to also analyse/present data from weeks 24 and 36 as more participants reached these timepoints.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for all participants from the date of consent until the participant's final trial assessment or up until the point of withdrawal where this was applicable.

Adverse event reporting additional description:

290 AEs were reported by 36 of the 39 participants included in the ITT population; 128 reported by 17/18 unique participants in the pramipexole arm and 162 by 19/21 in the placebo arm.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Pramipexole
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Reporting group description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Reporting group title	Placebo
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Reporting group description:

For all participants, initiation of trial treatment followed a 4-week titration schedule starting at 0.25mg/day in a single dose for 3 days. Thereafter the dose was increased by 0.25mg/day every 3 days. The target dose was 2.5mg/day but titration was based on tolerability and response.

Serious adverse events	Pramipexole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)	3 / 21 (14.29%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Foot surgery with overnight stay in hospital			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Mania and BAPD Relapse with Psychotic Symptoms			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe depressive episode with suicidality			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death, likely by suicide			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Pramipexole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	19 / 21 (90.48%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 18 (5.56%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	6 / 18 (33.33%)	6 / 21 (28.57%)	
occurrences (all)	7	8	
Immune system disorders			
Immune system disorders			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 21 (4.76%) 1	
Social circumstances Social circumstances subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	4 / 21 (19.05%) 4	
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 21 (4.76%) 2	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	14 / 18 (77.78%) 41	13 / 21 (61.90%) 53	
Investigations Investigations subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	3 / 21 (14.29%) 3	
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 6	7 / 21 (33.33%) 19	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	9 / 18 (50.00%) 17	10 / 21 (47.62%) 22	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 21 (4.76%) 1	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3	0 / 21 (0.00%) 0	
Gastrointestinal disorders			

Gastrointestinal disorders subjects affected / exposed occurrences (all)	10 / 18 (55.56%) 25	12 / 21 (57.14%) 28	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 6	0 / 21 (0.00%) 0	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 21 (4.76%) 2	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 21 (0.00%) 0	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	8 / 18 (44.44%) 14	10 / 21 (47.62%) 14	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 21 (9.52%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2019	<p>Updates made to some eligibility criteria. These updates were made for clarification purposes only and did not change the eligibility criteria itself. This impacted Pre-Randomisation Inclusion Criteria number 5, Pre-Randomisation Exclusion Criteria numbers 5, 10 and 11 and Randomisation Exclusion Criteria number 8 and 9.</p> <p>Full stability data for pramipexole was also available at this stage and this section of the protocol was therefore updated to reflect that there were no specific storage requirements for the trial medication.</p>
23 July 2020	<p>Protocol updated in response to COVID-19 to allow delivery to continue during government and local restrictions, without compromising participant safety or trial primary outcomes. This included removal of blood pressure and pulse measurements (as agreed by the DMC); allowing for pre-randomisation and randomisation screening activities to also be carried out remotely; ability for pre-randomisation and randomisation stage consent discussions to be conducted via telephone/teleconference or videoconference before the patient attends a shorter face to face clinic visit to complete the consent form; more options regarding collection of urine samples and returning of unused IMP.</p> <p>Pre-Randomisation inclusion criterion number 5 was also updated for clarification purposes only.</p>
20 October 2020	<p>Updates to allow further flexibility regarding how the participant can initially be approached and to provide sites and participants with a further option regarding collection of unused IMP/empty bottles.</p>
15 December 2020	<p>Inclusion criteria added to state that participants should be in the pre-randomisation stage for a minimum of 23 days to increase flexibility for those participants who already met the remaining inclusion criteria allowing them to progress to the randomisation stage promptly and not delay their treatment.</p>
18 February 2021	<p>This amendment included an update to the inclusion and exclusion criteria to allow participants to enter the trial whilst taking certain antipsychotics, which could be adjusted during the pre-randomisation stage to meet the eligibility criteria for Randomisation. This update was made following a meeting with the funder and had the full support of both the PPI group and Trial Steering Committee. The update was approved by the HTA funder committee and their scientific advisers following submission of a written proposal which demonstrated that the co-administration of pramipexole in combination with a limited number of antipsychotics would allow increased recruitment and retention to the trial without comprising clinical effectiveness or safety.</p>
27 May 2021	<p>Protocol updated to correct the dose of an antipsychotic that can be used in the trial; to allow researchers to use a wider range of communication methods and to provide greater clarification around the timing and nature of trial procedures.</p> <p>As the trial was paused from March to September 2020 (reducing the amount of time available for the trial to complete the pilot phase), this amendment also outlined that, with the agreement of the funder, the pilot could start again in October 2020 with an end date of October 2021.</p>

13 May 2022	<p>This amendment related to the early closure of the PAX-BD trial. The protocol was amended to reflect this change and confirmed that all participants would have the opportunity to be followed up to treatment week 12, including those currently in the pre-randomisation stage of the trial.</p> <p>As well as this there were updates to the inclusion and exclusion criteria to aid sites when randomising the remaining participants to the randomisation stage.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 March 2020	Temporary halt implemented due to COVID-19 pandemic. The study was re-started via Substantial Amendment 8 dated 10.08.2020.	10 August 2020

Notes:

Limitations and caveats

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

n/a

Notes: