



## Clinical trial results:

### A Phase IV Acceptability and Feasibility Trial of the Effects of Medication on Memory in Idiopathic Parkinson's Disease without Cognitive Impairment

#### Summary

EudraCT number	2012-000801-64
Trial protocol	GB
Global end of trial date	04 March 2015

#### Results information

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

#### Trial information

##### Trial identification

Sponsor protocol code	BTG001
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##### Additional study identifiers

ISRCTN number	ISRCTN39374171
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University Hospitals of North Midlands NHS Trust
Sponsor organisation address	Newcastle Road, Stoke-on-Trent, United Kingdom, ST4 6QG
Public contact	Dr Darren Clement, University Hospitals of North Midlands NHS Trust, 01782 675379, Darren.clement@uhns.nhs.uk
Scientific contact	Dr Darren Clement, University Hospitals of North Midlands NHS Trust, 01782 675379, Darren.clement@uhns.nhs.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	02 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2015
Global end of trial reached?	Yes
Global end of trial date	04 March 2015
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

This is a feasibility and acceptability trial designed to inform the following process / primary outcomes:

- to obtain estimates of memory performance which will inform a power calculation; data collected during ON and OFF research sessions
- to examine the efficacy of processes and procedures used to manage symptoms during the washout periods (assessed at the mid and end of study clinic visits, and the semi-structured interview administered at the end of the trial).

In addition there were several secondary outcomes including assessing the drop out rate, effectiveness of the recruitment strategy, identifying training needs of the team, establishing the likely staffing resources for a fully powered trial, validate the composition of the neuropsychological test battery, gather personal reflections of participants on their research experience and explore barriers to participation.

Protection of trial subjects:

Participants were required to have a recent blood sample to ensure the kidney and liver function was not impaired (Exclusion criteria included renal impairment and severe liver impairment).

Participants were given a 24 hour contact number should the participant encounter any problems during the study.

Background therapy:

Participants may (or may not) be receiving adjuvant therapy with L-dopa and / or a monoamine oxidase B inhibitor (such as rasagiline / AZILECT or selegiline/ ELDEPRYL, ZELAPAR).

Evidence for comparator: -

Actual start date of recruitment	23 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	12
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a single centre trial (based at University Hospital of North Midlands NHS Trust). Local GP practices and community pharmacists acted as Participant Identification Centres, passing on study details to potential participants.

### Pre-assignment

Screening details:

Screening visit assessments/questionnaires: Functional assessment of mental capacity by CI/PI, Informed consent, Mini-Mental State examination, Review inclusion/exclusion criteria, Physical exam, Vital signs (BP, pulse, respiration rate, temperature, weight, height), blood test, PD symptom assessment, Hospital depression and anxiety scale, mood.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor <sup>[1]</sup>

Blinding implementation details:

The PhD student /assessor was blind to the participants' medications during the trial and for the analysis period.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	ARM 1:Pramipexole followed by Ropinirole

Arm description:

The order of IMPs in treatment arm 1 is pramipexole prolonged release followed by ropinirole prolonged release.

Arm type	Change to the order of drugs
Investigational medicinal product name	Pramipexole prolonged release
Investigational medicinal product code	ATC N04BC05
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pramipexole prolonged release max. 3.15 mg once daily, min. 0.52mg once daily.

Investigational medicinal product name	Ropinirole prolonged release
Investigational medicinal product code	ATC N04BC04
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ropinirole prolonged release max. 12 mg once daily, min 2mg once daily

<b>Arm title</b>	ARM 2: Ropinirole followed by Pramipexole
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Arm description:

The order of IMPs in treatment arm 2 is ropinirole prolonged release followed by pramipexole prolonged release.

Arm type	Order of IMPs is reversed
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Investigational medicinal product name	Ropinirole prolonged release
Investigational medicinal product code	ATC N04BC04
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ropinirole prolonged release max. 12 mg once daily, min 2mg once daily

Investigational medicinal product name	Pramipexole prolonged release
Investigational medicinal product code	ATC N04BC05
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pramipexole prolonged release max. 3.15 mg once daily, min. 0.52mg once daily

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only the PhD student/assessor (who performed memory recollection assessments with the participant) was blinded to the participants trial drug.

<b>Number of subjects in period 1</b>	ARM 1:Pramipexole followed by Ropinirole	ARM 2: Ropinirole followed by Pramipexole
Started	10	12
Completed	7	9
Not completed	3	3
Adverse event, non-fatal	3	3

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
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Reporting group description:

Twenty two participants represents the number of participants randomised into the trial and received trial drugs.

A total of 28 participants consented into the study, however these were determined to be ineligible at the screening visit, and therefore did not participate in the trial or receive study drugs.

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age characteristics for 22 participants randomised into the trial and received trial drugs.			
Units: years			
arithmetic mean	65.7		
standard deviation	± 8.1	-	
Gender categorical			
Gender characteristics for 22 participants randomised into the trial and received trial drugs.			
Units: Subjects			
Female	6	6	
Male	16	16	

## End points

### End points reporting groups

Reporting group title	ARM 1:Pramipexole followed by Ropinirole
Reporting group description: The order of IMPs in treatment arm 1 is pramipexole prolonged release followed by ropinirole prolonged release.	
Reporting group title	ARM 2: Ropinirole followed by Pramipexole
Reporting group description: The order of IMPs in treatment arm 2 is ropinirole prolonged release followed by pramipexole prolonged release.	

### Primary: Provide estimates of memory performance which will inform a power calculation for a large randomised controlled trial (memory recollection data collected during ON- and OFF-medication research sessions)

End point title	Provide estimates of memory performance which will inform a power calculation for a large randomised controlled trial (memory recollection data collected during ON- and OFF-medication research sessions)
End point description: For the ON research session, medication was taken as usual roughly 60 minutes before the session. For the OFF session, medication was delayed prior to the memory recollection. Medication was resumed following completion of the memory recollection, according to criteria discussed with the CI/PI.	
End point type	Primary
End point timeframe: As per protocol, assessments (memory recollection) performed after a six week stabilisation period on IMP. Assessments were conducted both ON and OFF drug (the medication was withheld during the OFF session according to the half lives of the drug).	

End point values	ARM 1:Pramipexole followed by Ropinirole	ARM 2: Ropinirole followed by Pramipexole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7 <sup>[1]</sup>	9 <sup>[2]</sup>		
Units: Memory recall	7	9		

Notes:

[1] - All patients received both IMPs (order of IMPs randomised between 2 arms). 7 had pramipexole first.

[2] - All patients received both IMPs (order of IMPs randomised between 2 arms). 9 had ropinirole first.

### Statistical analyses

Statistical analysis title	Confidence interval ropinirole
Statistical analysis description: Acceptability and feasibility trial: The confidence interval around the mean difference in memory recollection between ON and OFF each IMP (trial drug) was calculated. Data from both arms was combined for the analysis.	
Comparison groups	ARM 1:Pramipexole followed by Ropinirole v ARM 2: Ropinirole followed by Pramipexole

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.084
Variability estimate	Standard deviation

Notes:

[3] - As this was a acceptability and feasibility trial, we were not concerned with statistical significance with regards to memory recollection as the group sizes were not large enough to detect a difference if it existed. It is important to note that at this stage in the program of research there is still no firm evidence that dopaminergic medication in particular pramipexole affects memory. Therefore people with Parkinson's should not change their medication based on this trial.

<b>Statistical analysis title</b>	Confidence interval pramipexole
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Statistical analysis description:

Acceptability and feasibility trial: The confidence interval around the mean difference in memory recollection between ON and OFF each IMP (trial drug) was calculated. Data from both arms was combined for the analysis.

Comparison groups	ARM 1:Pramipexole followed by Ropinirole v ARM 2: Ropinirole followed by Pramipexole
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.019
upper limit	0.079
Variability estimate	Standard deviation

Notes:

[4] - As this was a acceptability and feasibility trial, we were not concerned with statistical significance with regards to memory recollection as the group sizes were not large enough to detect a difference if it existed. It is important to note that at this stage in the program of research there is still no firm evidence that dopaminergic medication in particular pramipexole affects memory. Therefore people with Parkinson's should not change their medication based on this trial.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of informed consent to the participants' end of study visit with the Principle Investigator.

Adverse event reporting additional description:

Adverse events were collected at Mid and End of study visits by discussion with the participant. Participant had contact telephone numbers for the PI/research team and a 24 hour ward number as patient support. Please note all adverse events were collected (regardless of whether the adverse event was considered to be caused by the trial drug).

Assessment type	Systematic
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### Dictionary used

Dictionary name	WHO ICD10
Dictionary version	2016

### Reporting groups

Reporting group title	Pramipexole
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Reporting group description:

Participants who received any dose of pramipexole following patient consent

Reporting group title	Ropinirole
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Reporting group description:

Any participant who received any dose of ropinirole following consent.

Please note there was one additional participant who consented to the study, then had a adverse event to ropinirole (usual prescription). This participant was withdrawn and did not receive trial drugs.

Serious adverse events	Pramipexole	Ropinirole	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Pramipexole	Ropinirole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)	21 / 22 (95.45%)	
Vascular disorders			
Postural hypotension	Additional description: Includes "hypotension when sitting and standing"		
subjects affected / exposed	1 / 20 (5.00%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Thrombophlebitis	Additional description: Thrombophlebitis (swollen ankle)		

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
General disorders and administration site conditions			
Malaise	Additional description: Includes unwell and fatigue		
subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4	3 / 22 (13.64%) 3	
Excessive sweating subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Swollen extremities subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	3 / 22 (13.64%) 1	
Social circumstances Work related stress subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Respiratory, thoracic and mediastinal disorders			
Wheezing subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Breathlessness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Psychiatric disorders			
Sleep disorder	Additional description: Includes restless sleep, sleep disturbance, interrupted sleep, insomnia, increased aggressive sleeping behaviour.		
subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 5	1 / 22 (4.55%) 1	
Anxiety subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	3 / 22 (13.64%) 3	
Low mood	Additional description: In association with a medication error (insufficient dose of study drug taken)		

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Drowsiness subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	
Confusional state subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	1 / 22 (4.55%) 1	
Hallucinations subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	0 / 22 (0.00%) 0	
Investigations Weight gain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 22 (0.00%) 0	
Road Traffic accident subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Palpitations subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Nervous system disorders Tension headache subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	

Worsening Tremor subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	3 / 22 (13.64%) 3	
Increased jerky movements subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Increased Parkinson's symptoms subjects affected / exposed occurrences (all)	Additional description: Includes shaky from hand to foot. One report was in association with a medication error (insufficient dose of study drug taken).		
	0 / 20 (0.00%) 0	3 / 22 (13.64%) 3	
Coordination disorder subjects affected / exposed occurrences (all)	Additional description: Includes slow movements and tripping		
	0 / 20 (0.00%) 0	2 / 22 (9.09%) 2	
Vivid dreams subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 22 (9.09%) 0	
Memory impairment subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 22 (0.00%) 0	
Balance disorder subjects affected / exposed occurrences (all)	Additional description: In association with a fall		
	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Increased dizziness and giddiness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 22 (9.09%) 2	
Headache subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	
Ear and labyrinth disorders Otitis media subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 22 (0.00%) 0	
Ear wax subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Umbilical hernia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Bloating			
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Gagging			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Hiccups	Additional description: Increased hiccups		
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 20 (5.00%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Hypersensitivity rash			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Aching legs			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Back pain	Additional description: Exacerbation of back pain		
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Over eating			
subjects affected / exposed	2 / 20 (10.00%)	0 / 22 (0.00%)	
occurrences (all)	2	0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2013	Protocol 4: Changes Includes: <ul style="list-style-type: none"><li>• Addition of nearest dosage of tablets of pramipexole to medication conversation table (Protocol section 6.2.1).</li><li>• Update to appendix 5 (conversion table for transferring patients between trial treatments), reference used to match table in body of protocol.</li><li>• Exclusion criteria: clarification of hepatic impairment added (3X Upper limit of normal) for clarity.</li><li>• Exclusion criteria: Added all doses that fall outside inclusion criteria</li><li>• Updated process details for prescribing IMPs and pharmacy records</li><li>• Added the research nurse to phone patient 48 hours after starting IMP to monitor adverse events.</li><li>• Mid study visit: Blood tests to be performed if not completed in previous 3 months</li></ul>
03 September 2013	Amendment to IMP from branded drugs to use of generics (this was consistent with original Clinical Trial Authorisation from the MHRA)
20 January 2014	Protocol V6 changes includes: <ul style="list-style-type: none"><li>• Updates to IMPs (Pramipexole base (not salt) now referred to throughout the protocol, minor change to IMP conversion tables).</li><li>• Further pharmacy/prescribing related details updated.</li><li>• Pharmacy will keep records of destroyed IMPs</li><li>• Barriers to recruitment questionnaire sub study added</li></ul>
06 May 2014	Due to recruitment difficulties, use of Participant Identification Centres were added to the protocol. This amendment included new documents to support Participants to be identified via local GP practices.
06 May 2014	To further aid the identification of potential participants: Update to the protocol to include use of Community Pharmacies to raise awareness of the clinical trial (Participant Identification activity) Supportive documents for the barriers to recruitment sub-study approved
21 July 2014	<ul style="list-style-type: none"><li>• Clarifications to the consent process (PI to take consent)</li><li>• Amendment to perform the blood test at screening for all patients</li><li>• Changes to the emergency contact number</li><li>• New study documents include:</li><li>• New drug Swap trial cards (to ensure participants had written information regarding swapping from one IMP to the other).</li></ul>
23 October 2014	Request to temporarily halt recruitment accepted by MHRA. An error was identified in the patient information sheet regarding the side effect profile of the study drugs. Decision made by sponsor to temporarily halt further recruitment until the patient information sheet had been corrected.

28 October 2014	<p>REC accepted temporarily halt to recruitment and approved new documentation. MHRA accepted updated protocol, change to reference safety information and trial restart on 10-Dec-2014.</p> <ul style="list-style-type: none"> <li>Update to reference safety information (RSI) (from section 4.8 of the summary of product characteristics (SmPC) Requip XL April 2012 to the latest available SPC 13 March 2014 and from section 4.8 Mirapexin 1.05mg prolonged release July 2011 (one dosage selected) to the latest available Mirapexin 3.15mg prolonged release February 2014.</li> <li>Clarification to inclusion / Exclusion criteria: Inclusion criteria clarified that patients who are not receiving adjuvant therapy also meet the inclusion criteria Added detail of the liver function tests examined locally (for clarity) Renal impairment exclusion criteria is clarified to be creatinine clearance or eGFR. Clarification that planned or current participation in a drug trial is not permitted</li> <li>Mid visit assessment on mental capacity As per the recommendation of the CI/PI, the mini mental state examination will not be repeated at mid visit as failing some aspects of the test can be upsetting to the patient. Clinical judgement will be used to assess that the patient has mental capacity to continue.</li> <li>Correction to side effect profile of the IMPs (protocol and Patient information Sheet) Section 7.5.1 of protocol now includes the section 4.8 of the RSI for both IMPs</li> <li>Minimum stabilisation period on IMP stated as 4 weeks.</li> <li>Correction to Patient Information Sheet regarding the side effect profile of the IMPs.</li> </ul>
28 October 2014	Approval of two (monotherapy and adjuvant therapy) patient letters describing the error in patient information sheet concerning the incorrect side effect profile of the IMPs.
28 November 2014	REC approved Trial restart. MHRA approved trial restart on 10-December-2014 (along with the updated protocol) (see REC amendment dated 28-Oct-2014)

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 September 2014	Note trial temporarily stopped from 22-Sep-2014 to 18-Dec-2014 due to an error identified in the participant information sheet regarding errors in the side effect profile of the trial drugs in the participant information sheet. This error was rectified and the trial was restarted on 18-Dec-2014.	18 December 2014

Notes:

## Limitations and caveats

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

The trial failed to meet the target recruitment of 50 participants. This was a feasibility study and a number a protocol deviations were reported. People with Parkinson's should not change their medication based on this trial.

Notes:



