Clinical trial results:
Simvastatin as a neuroprotective treatment for Parkinson's disease: a double-blind, randomised, placebo controlled futility study in patients of moderate severity.

Summary

EudraCT number	2015-000148-40
Trial protocol	GB
Global end of trial date	05 June 2020

Results information

Result version number	v1 (current)
This version publication date	03 June 2021
First version publication date	03 June 2021

Trial information

Trial identification

Sponsor protocol code	PDSTAT2015

Additional study identifiers

ISRCTN number	ISRCTN16108482
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference: 15/NE/0324, IRAS Number: 172703, UHPNT R&D Reference Number: 14/P/125

Notes:

Sponsors

Sponsor organisation name	University Hospitals Plymouth NHS Trust
Sponsor organisation address	Research Office, L2 MSCP, Bircham Park Offices, 1 Roscoff Rise, Derriford, Plymouth, United Kingdom, PL6 5FP
Public contact	Dr Alison Jeffery, Trial Manager , Peninsula Clinical Trials Unit (PenCTU), Faculty of Medicine and Dentistry, University of Plymouth, 01752 439831, PenCTU@plymouth.ac.uk
Scientific contact	Dr Camille Carroll, Associate Professor and Honorary Consultant Neurologist, Peninsula Medical School, Faculty of Medicine and Dentistry University of Plymouth , 01752 439829, camille.carroll@plymouth.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	06 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2020
Global end of trial reached?	Yes
Global end of trial date	05 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether simvastatin is clearly ineffective (futile) in preventing the clinical decline of PD as measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score.

Protection of trial subjects:

The study is approved by the MHRA, the North East - Newcastle & North Tyneside 2 Research Ethics Committee (NRES) and the Health Research Authority (HRA). Study monitoring is conducted by the Peninsula Clinical Trials Unit (PenCTU) and an Independent Trial Steering Committee (TSC), Trial Management Group (TMG) and Data Monitoring Committee (DMC) are set up for the study oversight.

Background therapy:

Levodopa.

Evidence for comparator:

The active investigational medicinal product is simvastatin. Active trial medication will be provided as simvastatin 40mg for the first month then 80mg for the following 23 months with cellulose microcrystalline powder in capsule form, to be taken orally. The comparator is a matched placebo capsule containing cellulose microcrystalline powder only.

Actual start date of recruitment	01 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	26 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 235
Worldwide total number of subjects	235
EEA total number of subjects	235

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)	105
From 65 to 84 years	125
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Patients will be recruited over 12 months from clinical lists, through research registrars, publicity and word of mouth.

Pre-assignment

Screening details:

Demographic information and medical history. Concomitant medication and 'wearing-off' questionnaire. Provide "Wearing off guide for patients" (for participant to take home). Physical examination (inc. assessment of modified Hoehn & Yahr stage). MoCA. MADRS. Blood samples for: CK, AST, ALT, eGFR, HDL total, TSH, HbA1C, urea and electrolytes.

Period 1

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

Blinding implementation details:

Statistical analyses completed blinded before allocation groups were revealed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo capsules containing cellulose microcrystalline power, taken orally.

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

Dosage and administration details:

The comparator is a matched placebo capsule containing cellulose microcrystalline powder only.

Medication will be prescribed in two phases: a lower dose phase of 40 mg active drug/equivalent placebo for one month and a higher dose maintenance phase of 80 mg active drug/equivalent placebo for 23 months.

Investigational medicinal product name	cellulose microcrystalline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Medication will be prescribed in two phases: a lower dose phase of 40 mg active drug/equivalent placebo for one month and a higher dose maintenance phase of 80 mg active drug/equivalent placebo for 23 months.

The comparator is a matched placebo capsule containing cellulose microcrystalline powder only.

Arm title	Simvastatin

Arm description:

Participants received simvastatin 40mg with cellulose microcrytalline powder in capsule form, taken orally.

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

Dosage and administration details:

The active investigational medicinal product is simvastatin. Active trial medication will be provided as simvastatin 40mg with cellulose microcrystalline powder in capsule form, to be taken orally.

Medication will be prescribed in two phases: a lower dose phase of 40 mg active drug/equivalent placebo for one month and a higher dose maintenance phase of 80 mg active drug/equivalent placebo for 23 months.

Number of subjects in period 1	Placebo	Simvastatin
Started	118	117
Completed	90	88
Not completed	28	29
Adverse event, serious fatal	2	1
Consent withdrawn by subject	18	18
Invalid outcome measure	2	5
Did not progress to high dose	4	3
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo capsules containing cellulose microcrystalline power, taken orally.	
Reporting group title	Simvastatin
Reporting group description:	
Participants received simvastatin 40mg with cellulose microcrytalline powder in capsule form, taken orally.	

Reporting group values	Placebo	Simvastatin	Total
Number of subjects	118	117	235
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			
Units: years			
arithmetic mean	65.0	65.9	
standard deviation	± 9.7	± 8.7	-
Gender categorical			
Units: Subjects			
Female	52	45	97
Male	66	72	138
Hoehn and Yahr Startification			
Hoehn and Yahr stratification variable used to randomize participants to treatment group			
Units: Subjects			
1.0 to 2.0	80	82	162
2.5 to 3.0	38	35	73
PD disease duration			
Number of years since onset of PD			
Units: years			
arithmetic mean	10.0	9.6	
standard deviation	± 4.8	± 3.8	-
MDS-UPDRS part III (OFF)			
MDS-UPDRS part III (OFF) measured at baseline using valid imputation, i.e. imputation for a maximum of 3 missing items. Placebo n = 115 and simvastatin n = 112.			
Units: score			
arithmetic mean	35.1	33.3	
standard deviation	± 13.8	± 13.7	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo capsules containing cellulose microcrystalline power, taken orally.	
Reporting group title	Simvastatin
Reporting group description:	
Participants received simvastatin 40mg with cellulose microcrytalline powder in capsule form, taken orally.	

Primary: Change in MDS-UPDRS Part III (Off)

End point title	Change in MDS-UPDRS Part III (Off)
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to 24 months	

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[1]	88[2]		
Units: Score				
arithmetic mean (standard deviation)	2.4 (± 11.2)	4.5 (± 12.2)		

Notes:

[1] - Progressed to the high dose with valid MDS-UPDRS part III (OFF) at baseline and 24 months

[2] - Progressed to the high dose with valid MDS-UPDRS part III (OFF) at baseline and 24 months

Statistical analyses

Statistical analysis title	Mixed effects linear regression model
Statistical analysis description:	
A mixed effects linear regression model was fitted to the change in MDS-UPDRS part III (OFF) from baseline to 24 months, with adjustments for baseline MDS-UPDRS part III (OFF), age and PD duration at baseline, sex, and Hoehn & Yahr stratification as fixed effects and study centre as a random effect.	
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.006 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.52

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.77
upper limit	3.8
Variability estimate	Standard error of the mean
Dispersion value	1.78

Notes:

[3] - Futility analysis of the mean between-group difference (placebo - simvastatin) estimated from the mixed effects linear regression model. Rejection of the null hypothesis indicates intervention futility.
[4] - Null hypothesis: mean between-group difference (placebo - simvastatin) = -3
Alternate hypothesis: mean between-group difference (placebo - simvastatin) > -3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo and simvastatin combined

Reporting group description: -

Serious adverse events	Placebo and simvastatin combined		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 228 (21.49%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
subjects affected / exposed	3 / 228 (1.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgical and medical procedures	Additional description: Surgical and medical procedures		
subjects affected / exposed	20 / 228 (8.77%)		
occurrences causally related to treatment / all	0 / 26		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: General disorders and administration site conditions		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: Respiratory, thoracic and mediastinal disorders		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Investigations			
Investigations	Additional description: Investigations		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: Injury, poisoning and procedural complications		
subjects affected / exposed	8 / 228 (3.51%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders	Additional description: Cardiac disorders		
subjects affected / exposed	5 / 228 (2.19%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorders	Additional description: Nervous system disorders		
subjects affected / exposed	5 / 228 (2.19%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye disorders	Additional description: Eye disorders		
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: Gastrointestinal disorders		
subjects affected / exposed	7 / 228 (3.07%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: Hepatobiliary disorders		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: Renal and urinary disorders		
subjects affected / exposed	3 / 228 (1.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Endocrine disorders	Additional description: Endocrine disorders		
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations	Additional description: Infections and infestations		
subjects affected / exposed	4 / 228 (1.75%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo and simvastatin combined		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 228 (32.02%)		
Investigations			
Investigations	Additional description: Investigations		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences (all)	6		
Vascular disorders			
Vascular disorders	Additional description: Vascular disorders		
subjects affected / exposed	1 / 228 (0.44%)		
occurrences (all)	2		
Cardiac disorders			

Cardiac disorders	Additional description: Cardiac disorders		
subjects affected / exposed	1 / 228 (0.44%)		
occurrences (all)	3		
Nervous system disorders			
Nervous system disorders	Additional description: Nervous system disorders		
subjects affected / exposed	10 / 228 (4.39%)		
occurrences (all)	38		
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: General disorders and administration site conditions		
subjects affected / exposed	13 / 228 (5.70%)		
occurrences (all)	38		
Eye disorders			
Eye disorders	Additional description: Eye disorders		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences (all)	4		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: Gastrointestinal disorders		
subjects affected / exposed	17 / 228 (7.46%)		
occurrences (all)	52		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: Respiratory, thoracic and mediastinal disorders		
subjects affected / exposed	3 / 228 (1.32%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: Skin and subcutaneous tissue disorders		
subjects affected / exposed	4 / 228 (1.75%)		
occurrences (all)	10		
Psychiatric disorders			
Psychiatric disorders	Additional description: Psychiatric disorders		
subjects affected / exposed	2 / 228 (0.88%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: Musculoskeletal and connective tissue disorders		
subjects affected / exposed	46 / 228 (20.18%)		
occurrences (all)	157		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2015	Protocol updated to v2.0 Kings College Hospital, London, added as a participating site and amendment to enable the use of Participant Identification Centres.
17 November 2015	No change to study protocol. Simplified Investigational Medicinal Product Dossier amended to fulfil condition of the CTA application for the study.
19 February 2016	No change to study protocol. Change to Principal Investigator at Musgrove Park Hospital, Taunton.
23 March 2016	Protocol updated to version 3.2 to clarify details of qualitative sub study following confirmation of additional funding.
21 July 2016	Protocol updated to version 3.3 to clarify target population being approached for qualitative sub study and to bring study under HRA approval.
20 January 2017	No change to protocol. Change to Principal Investigator at Clinical Ageing Research Unit, Newcastle.
20 February 2017	No change to protocol. New documents for approval for qualitative sub study and amended documents for genetic sub study.
28 March 2017	Modification of previous amendment following unfavourable opinion from REC. Carer focus group documents removed from the amendment.
27 April 2017	Protocol updated to version 4.1 to electro magnetic sensor measurement sub study and other administrative changes.
31 July 2017	Addition of 3 new study sites: Rotherham Hospital, Royal Stoke University Hospital and Royal Berkshire Hospital.
24 April 2018	Addition of study newsletters to be sent to participants twice a year.
27 July 2018	Change to Principal Investigator at Royal Preston Hospital.
21 November 2018	Change to Principal Investigator at Leeds General Infirmary.
26 November 2018	Update to SmPC, protocol updated to version 4.3, updated study documentation and addition of end of study postcards.
30 January 2019	Protocol updated to version 4.4 to include: GP letter re updated medication recommendations; End of study GP letter; Addition of EMS measurement at 26 weeks; Home visits.
22 April 2020	Protocol updated to version 4.6 to include addition of qualitative sub study comprising survey and semi structured interviews for site staff.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported