Clinical trial results:
Does Co-careldopa treatment in combination with routine NHS occupational and physical therapy, delivered early after stroke within a stroke service, improve functional recovery including walking and arm function?

Summary

EudraCT number	2009-017925-20
Trial protocol	GB
Global end of trial date	18 May 2015

Results information

Result version number	v1 (current)
This version publication date	08 May 2016
First version publication date	08 May 2016

Trial information

Trial identification

Sponsor protocol code	RR08/8789

Additional study identifiers

ISRCTN number	ISRCTN99643613
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Hyde Terrace, Leeds, United Kingdom, LS2 9LN
Public contact	QA Department, University of Leeds, ctruq@leeds.ac.uk
Scientific contact	QA Department, University of Leeds, ctruq@leeds.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	18 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2015
Global end of trial reached?	Yes
Global end of trial date	18 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if combining Co-careldopa with routine occupational and physical therapy during early rehabilitation in people with new stroke admitted to a stroke unit enhances the effect of conventional rehabilitation treatments in terms of physical functioning.
The primary objective compared the proportion of patients walking independently at eight weeks post-randomisation.
Secondary objectives were to assess the impact on physical functioning, mood and cognition at eight weeks, six months and 12 months post randomisation comparing between treatment groups.

Protection of trial subjects:

Protection of trial subjects:
The trial subjects were recruited as in patients at acute stroke rehabilitation facilities within hospital Trusts. They were monitored closely as part of their hospital inpatient care plan. Where appropriate some services enabled patients to be discharged into the community where they were supported by the early discharge team.

Administration of the first two doses of the trial IMP (Co-careldopa/placebo tablets) were taken whilst the patient was in hospital and under the supervision of a clinician. The first two doses were lower doses to reduce the risk of early adverse events.

Follow up visits were conducted face to face in the patient's home, at hospital or at a research facility. When face to face contact was not possible, a telephone follow up was conducted.

CTRU prepared 6-monthly safety reports during the recruitment and follow up period for review by the Data Monitoring Ethics Committee. Also, DMEC reviewed 3-monthly un-blinded reports which included a summary of SAEs, SARs and SUSARs summarised by treatment groups.

Trial data was collected on paper CRFs and were sent to the CTRU where it was entered onto a trial database application - MACRO. The database is stored on a private network protected by a firewall. Access is restricted to trial staff by login and password. The trial data was then filed in locked filling cabinets.

CTRU will comply with all aspects of Data Protection Act 1998. All information collected during the trial will be kept strictly confidential. Patient names were collected on the consent form. However, for all other data collection forms that were transferred to or from CTRU the data was coded with a trial number, the patient's initials and date of birth.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 May 2011
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: 593
Worldwide total number of subjects	593
EEA total number of subjects	593

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)	205
From 65 to 84 years	322
85 years and over	66

Subject disposition

Recruitment

Recruitment details:

Patient admitted to stroke services after a new or recurrent stroke were approached and considered for enrolment from 5 to 42 days post stroke. Between May 2011 and March 2014, 593 patients (mean age 68.5 years, 364 (61.4%) male) and 165 carers (mean age 59.7 years, 47 (28.5%) male) were recruited.

Pre-assignment

Screening details:

During the recruitment period, 19509 patients were screened for eligibility. Of those screened, 1547 (7.9%) were deemed eligible, 599 (3.1%) were consented and 593 (3.0%) were randomised.

Pre-assignment period milestones

Number of subjects started	19509[1]
Number of subjects completed	593

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible: 17962
Reason: Number of subjects	Not consented: 948
Reason: Number of subjects	Not randomised: 6

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: These are patients screened for eligibility and were not consented into the trial.

Period 1

Period 1 title	Main trial (baseline-8 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

A placebo tablet was manufactured to match the commercial Co-careldopa (Sinemet®), and the final assembly, packaging and labelling of the co-careldopa / placebo kit was performed by Sharp Clinical Services. The composition of the placebo was approved by the MHRA. Co-careldopa and matching placebo were labelled with a unique random 5 digit kit number, which was assigned to a participant upon randomisation by the central randomisation system at the CTRU.

Arms

Are arms mutually exclusive?	Yes
Arm title	Co-careldopa

Arm description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Arm type	Active comparator

Investigational medicinal product name	Co-careldopa
Investigational medicinal product code	
Other name	Sinemet®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were randomised to receive either Co-careldopa (Sinemet®) or matched Placebo tablet in addition to routine NHS physical therapy (PT) and occupational therapy (OT). The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).

Arm title	Placebo

Arm description:

Control arm

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:

Patients were required to take placebo as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Number of subjects in period 1	Co-careldopa	Placebo
Started	308	285
Completed	271	261
Not completed	37	24
Moved out of area	1	1
Withdrawn	24	11
Not known	-	4
Other	1	-
Could not contact	-	2
Lost in post	-	1
Too unwell	1	2
Lost at site	4	-
Died	6	1
Refused to complete	-	2

Period 2

Period 2 title	6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Co-careldopa

Arm description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Arm type	Active comparator
Investigational medicinal product name	Co-careldopa
Investigational medicinal product code	
Other name	Sinemet®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were randomised to receive either Co-careldopa (Sinemet®) or matched Placebo tablet in addition to routine NHS physical therapy (PT) and occupational therapy (OT). The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).

Arm title	Placebo

Arm description:

Control arm

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:

Patients were required to take placebo as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Number of subjects in period 2	Co-careldopa	Placebo
Started	271	261
Completed	242	250
Not completed	29	11
Withdrawn	6	4
Other	16	1
Died	7	6

Period 3

Period 3 title	12 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Co-careldopa

Arm description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Arm type	Active comparator
Investigational medicinal product name	Co-careldopa
Investigational medicinal product code	
Other name	Sinemet®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were randomised to receive either Co-careldopa (Sinemet®) or matched Placebo tablet in addition to routine NHS physical therapy (PT) and occupational therapy (OT). The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).

Arm title	Placebo

Arm description:

Control arm

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:

Patients were required to take placebo as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Number of subjects in period 3	Co-careldopa	Placebo
Started	242	250
Completed	222	221
Not completed	20	29
Withdrawn	12	7
Other	-	12
Died	8	10

Baseline characteristics

Reporting groups

Reporting group title	Co-careldopa

Reporting group description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Reporting group title	Placebo

Reporting group description:

Control arm

Reporting group values	Co-careldopa	Placebo	Total
Number of subjects	308	285	593
Age categorical Units: Subjects			
Adults (18-64 years)	113	92	205
From 65-84 years	161	161	322
85 years and over	34	32	66
Age continuous Units: years			
arithmetic mean	67.5	69.6	
standard deviation	± 13.65	± 12.68	-
Gender categorical Units: Subjects			
Female	121	108	229
Male	187	177	364
Type of stroke Units: Subjects			
Infarction	270	238	508
Primary haemorrhage	38	47	85
Education Units: Subjects			
</= 12 years	134	139	273
>12 years	168	140	308
Missing	6	6	12
Thrombolysis received Units: Subjects			
Yes	62	59	121
No	208	178	386
Missing	0	1	1
Not applicable	38	47	85
Type of scan Units: Subjects			
CT brain scan	299	281	580

brain MRI	9	4	13
Missing	0	0	0
Not applicable	0	0	0
Digital scans Units: Subjects			
Yes	263	250	513
No	35	31	66
Missing	1	0	1
Not applicable	9	4	13
Rivermead Mobility Index (RMI) - researcher completed			
RMI assesses ability to walk independently. It was completed by researchers prior to randomisation to inform the stratification of patients. It has 15 items (score range 0-15), with higher scores indicating increased ability to walk independently.			
Units: Subjects			
Score 0-3	237	223	460
Score >3 but <7	71	62	133
General health questionnaire 12 (GHQ12)			
GHQ-12 assesses emotional health. It contains 12 questions (score range 0-36) addressing issues of decision making, loss of sleep and confidence, feelings of strain, enjoyment of daily activities, confidence and happiness. A higher score indicates worse emotional health. The scores can also be categorised into: no sign of psychological distress; evidence of distress (score >15); severe problems and psychological distress (score >20).			
Units: Subjects			
No sign of psychological distress	91	94	185
Evidence of distress	85	68	153
Severe problems and psychological distress	117	115	232
Missing	15	8	23
Montreal Cognitive Assessment (MoCA)			
MoCA is a researcher-administered instrument that assesses cognitive function. It contains 10 items and the scores range from 0 to 30; a score <26 indicates cognitive impairment.			
Units: Subjects			
Normal	57	63	120
Cognitive impairment	242	218	460
Missing	9	4	13
Rivermead Mobility Index (RMI score) - researcher completed			
RMI assesses ability to walk independently. It was completed by researchers prior to randomisation to inform the stratification of patients at baseline. It has 15 items (score range 0-15), with higher scores indicating increased ability to walk independently			
Units: Score			
arithmetic mean	2.2	2.3	
standard deviation	± 1.8	± 1.8	-
Montreal Cognitive Assessment (MoCA)			
MoCA is a researcher-administered instrument that assesses cognitive function. It contains 10 items and the scores range from 0 to 30; a score <26 indicates cognitive impairment.			
Units: Score			
arithmetic mean	20	20.5	
standard deviation	± 6.6	± 6	-
Rivermead Mobility Index (RMI score) - patient completed			
RMI assesses ability to walk independently. It was completed by participants at baseline and follow-up to see how they assessed their own mobility. It has 15 items (score range 0-15), with higher scores indicating increased ability to walk independently			
Units: Score			

arithmetic mean	2.4	2.5	
standard deviation	± 2.2	± 2.2	-
ABILHAND Scale			
The ABILHAND questionnaire measures upper limb impairment by asking participants to rate 23 items relating to their manual ability on a 3 level scale (impossible, difficult, easy). The raw scores are converted into a linear measure of ability using Rasch analysis. The scores are thus expressed as logits on an interval scale ranging from plus to minus with the centre of the scale set to zero. A higher number logit indicates greater patient's perceived ability. The baseline score in DARS is based on participant's own assessment of their manual ability in the month before their stroke.			
Units: Logits			
arithmetic mean	0.8	0.3	
standard deviation	± 3.9	± 1.8	-
Nottingham Extended Activities of Daily Living (NEADL) Scale			
Physical and social independence were assessed using NEADL. It assesses aspects of physical and social independence performance across 22 items (score range 0-66) grouped into four categories (mobility, kitchen, domestic and leisure activities); a higher score indicates greater independence. At baseline, participants were asked to consider their independence before their stroke and in the last month at the follow-up.			
Units: Score			
arithmetic mean	59	58.6	
standard deviation	± 11	± 12.4	-
Barthel Index			
Activities of daily living, disability and mobility were assessed using the Barthel Index. Ten items (score range 0-20) evaluate the patient's functional ability; higher scores indicate a greater degree of functional independence.			
Units: Score			
arithmetic mean	7.7	7.8	
standard deviation	± 8.3	± 3.7	-
Montreal Cognitive Assessment (MoCA)			
MoCA is a researcher-administered instrument that assesses cognitive function. It contains 10 items and the scores range from 0 to 30; a score <26 indicates cognitive impairment.			
Units: score			
arithmetic mean	20	20.5	
standard deviation	± 6.6	± 6	-
General health questionnaire 12 (GHQ12)			
GHQ-12 assesses emotional health. It contains 12 questions (score range 0-36) addressing issues of decision making, loss of sleep and confidence, feelings of strain, enjoyment of daily activities, confidence and happiness. A higher score indicates worse emotional health.			
Units: Score			
arithmetic mean	19.4	19.3	
standard deviation	± 6.7	± 7	-

End points

End points reporting groups

Reporting group title	Co-careldopa

Reporting group description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Reporting group title	Placebo

Reporting group description:

Control arm

Reporting group title	Co-careldopa

Reporting group description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Reporting group title	Placebo

Reporting group description:

Control arm

Reporting group title	Co-careldopa

Reporting group description:

Active arm
The initial two doses of Co-careldopa were 62.5mg (Levodopa 50mg and carbidopa 12.5mg) and the remaining doses were 125mg (Levodopa 100mg and carbidopa 25mg).
Patients were required to take it as a single oral tablet 45-60 minutes before PT or OT sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS was defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy).

Reporting group title	Placebo

Reporting group description:

Control arm

Primary: Rivermead Mobility Index (RMI) categorical - 8 weeks

End point title	Rivermead Mobility Index (RMI) categorical - 8 weeks

End point description:

The primary endpoint is the ability to walk independently at 8 weeks post-randomisation (defined by a score of 7 or above and who also answer 'yes' to item number 7 on the Rivermead Mobility Index questionnaire.
For the primary outcome ITT (intention to treat)analysis, it was assumed that patients who died or were lost to follow-up were unable to walk independently.

End point type	Primary

End point timeframe:

Number of patients walking independently at 8 weeks post randomisation.

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	285		
Units: number of patients				
Able to walk independently at 8 weeks	125	127		
Not able to walk independently at 8 weeks	183	158		

Statistical analyses

Statistical analysis title	Stepwise multilevel logistic regression analysis

Statistical analysis description:

For the primary outcome ITT analysis, it was assumed that patients who died or were lost to follow-up were unable to walk independently. The planned analyses for estimating differences in walking ability between treatment groups (Co-careldopa and placebo) were to use a multi-level logistic regression model adjusted for stratification variables: gender, type of stroke, researcher-completed RMI baseline score (continuous) and centre (the latter fitted as a random effect). Continued, see comment.

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	593
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.212
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.528
upper limit	1.153

Notes:

[1] - inspection of the residuals, influence and model fit statistics and the diagnostic plots suggested poor model fit, therefore stepwise regression that additionally included age, baseline scores for Barthel Index, ABILHAND, NEADL, MoCA and GHQ-12, number of days between stroke and randomisation, and total number of sufficient motor therapy sessions was used to build a more robust model.

Secondary: Modified Rankin Scale - 8 weeks

End point title	Modified Rankin Scale - 8 weeks

End point description:

End point type	Secondary

End point timeframe:

at 8 weeks

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: number of patients				
cat 0	3	1		
cat 1	15	11		
cat 2	24	30		
cat 3	101	114		
cat 4	95	79		
cat 5	34	34		
cat 6	6	1		

Statistical analyses

Statistical analysis title	stepwise multilevel ordinal logistic regression
Statistical analysis description:	
model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline NEADL score, baseline Barthel index and days between stroke and randomisation	
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.404
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.871
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.629
upper limit	1.206

Secondary: Montreal Cognitive Assessment (MOCA) - 8 weeks

End point title	Montreal Cognitive Assessment (MOCA) - 8 weeks
End point description:	
End point type	Secondary
End point timeframe:	
at 8 weeks	

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: Points				
arithmetic mean (standard deviation)	22.4 (± 6.26)	22.9 (± 5.51)		

Statistical analyses

Statistical analysis title	stepwise multilevel regression analysis
Statistical analysis description:	
covariates in the model: treatment arm, gender, stroke type, RMI score at randomisation, baseline MoCA, age, baseline NEADL, baseline ABILHAND and days between stroke and randomisation	
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.592
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.747
upper limit	0.427

Secondary: ABILHAND Scale - 8 week

End point title	ABILHAND Scale - 8 week
End point description:	
End point type	Secondary
End point timeframe:	
at 8 weeks	

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: logits				
arithmetic mean (standard deviation)	3.2 (± 7.8)	2.1 (± 6.5)		

Statistical analyses

Statistical analysis title	Stepwise multilevel linear regression analysis
Statistical analysis description:	
model was adjusted for gender, stroke type, RMI score at randomisation, baseline ABILHAND, baseline Barthel index, baseline MoCA, baseline NEADL, days between stroke and randomisation	
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.458
upper limit	0.259

Secondary: Nottingham Extended Activities of Daily Living (NEADL) Scale - 8 weeks

End point title	Nottingham Extended Activities of Daily Living (NEADL) Scale - 8 weeks
End point description:	
End point type	Secondary
End point timeframe:	
at 8 weeks	

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: Points				
arithmetic mean (standard deviation)	21 (± 17.7)	20 (± 15.8)		

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression analysis
Statistical analysis description:	
model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline NEADL score, baseline MoCA, baseline Barthel index and days between stroke and randomisation	
Comparison groups	Co-careldopa v Placebo

Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.382
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.238
upper limit	3.303

Secondary: General Health Questionnaire 12 - at 8 weeks

End point title	General Health Questionnaire 12 - at 8 weeks
End point description:	

End point type	Secondary
End point timeframe:	
at 8 weeks	

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: points				
arithmetic mean (standard deviation)	16.9 (± 7.2)	16.4 (± 6.6)		

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression analysis
Statistical analysis description:	
model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline GHQ12 score, baseline NEADL and baseline Barthel index	
Comparison groups	Placebo v Co-careldopa
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.677
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.238

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.884
upper limit	1.361

Secondary: Barthel Index at 8 weeks

End point title	Barthel Index at 8 weeks

End point description:

End point type	Secondary

End point timeframe:

8 weeks post randomisation

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: points				
arithmetic mean (standard deviation)	12.9 (± 5.09)	13.2 (± 4.9)		

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression

Statistical analysis description:

Model was adjusted for following covariates: treatment group, gender, stroke type, RMI score at randomisation, age, baseline NEADL score, baseline MoCA, baseline Barthel Index, days between stroke and randomisation.

Comparison groups	Placebo v Co-careldopa
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.511
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.218
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.868
upper limit	0.433

Secondary: Fatigue Assessment Scale - 8 weeks

End point title	Fatigue Assessment Scale - 8 weeks

End point description:

End point type	Secondary

End point timeframe:
at 8 weeks

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: Points				
arithmetic mean (standard deviation)	25.1 (± 7.6)	24.8 (± 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rivermead Mobility Index (RMI) continuous - 6 months

End point title	Rivermead Mobility Index (RMI) continuous - 6 months

End point description:

End point type	Secondary

End point timeframe:
Rivermead Mobility Index at 6 months as continuous

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[2]	250[3]		
Units: points				
arithmetic mean (standard deviation)	8.3 (± 4.6)	8.1 (± 4.5)		

Notes:
[2] - Please, note that number of subjects that started the arm was 308 (baseline).
[3] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression

Statistical analysis description:
the same covariates in the model were used as per primary endpoint analysis

Comparison groups	Co-careldopa v Placebo

Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.662
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.144
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.504
upper limit	0.791

Secondary: Barthel Index at 6 months

End point title	Barthel Index at 6 months

End point description:

End point type	Secondary

End point timeframe:

Barthel Index - 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[4]	250[5]		
Units: points				
arithmetic mean (standard deviation)	12.9 (± 5.1)	13.2 (± 4.9)		

Notes:

[4] - Please, note that number of subjects that started the arm was 308 (baseline).

[5] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	Stepwise multilevel linear regression analysis

Statistical analysis description:

Adjusted for gender, stroke type, RMI score at randomisation, age, baseline Barthel index, baseline MoCA score, baseline NEADL and days between stroke and randomisation

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.378
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.334

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.079
upper limit	0.41

Secondary: ABILHAND Scale - 6 months

End point title	ABILHAND Scale - 6 months

End point description:

End point type	Secondary

End point timeframe:

ABILHAND Scale - 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[6]	250[7]		
Units: logits				
arithmetic mean (standard deviation)	5.1 (± 9.4)	3.4 (± 8)		

Notes:

[6] - Please, note that number of subjects that started the arm was 308 (baseline).

[7] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	multilevel linear regression analysis
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.478
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.152
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.573
upper limit	0.269

Secondary: Nottingham Extended Activities of Daily Living (NEADL) Scale - 6 months

End point title	Nottingham Extended Activities of Daily Living (NEADL) Scale - 6 months

End point description:

End point type	Secondary

End point timeframe:

at 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[8]	250[9]		
Units: points				
arithmetic mean (standard deviation)	27.2 (± 18.2)	27.3 (± 18.1)		

Notes:

[8] - Please, note that number of subjects that started the arm was 308 (baseline).

[9] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	multilevel linear regression analysis

Statistical analysis description:

model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline NEADL score, baseline MoCA, baseline Barthel index and days between stroke and randomisation

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.724
upper limit	2.777

Secondary: General Health Questionnaire 12 - at 6 months

End point title	General Health Questionnaire 12 - at 6 months

End point description:

End point type	Secondary

End point timeframe:

at 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[10]	250[11]		
Units: points				
arithmetic mean (standard deviation)	15.1 (± 7)	16.3 (± 6.8)		

Notes:

[10] - Please, note that number of subjects that started the arm was 308 (baseline).

[11] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression analysis

Statistical analysis description:

model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline GHQ12 score, baseline NEADL and baseline Barthel index

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.332
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.569
upper limit	-0.096

Secondary: Modified Rankin Scale - 6 months

End point title	Modified Rankin Scale - 6 months

End point description:

End point type	Secondary

End point timeframe:

at 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[12]	250[13]		
Units: number of patients				
cat 0	1	2		
cat 1	29	25		
cat 2	23	30		
cat 3	123	128		
cat 4	41	47		

cat 5	27	16		
cat 6	6	4		

Notes:

[12] - Please, note that number of subjects that started the arm was 308 (baseline).

[13] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	stepwise multilevel ordinal logistic regression

Statistical analysis description:

model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline NEADL score, baseline Barthel index and days between stroke and randomisation

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.808
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.571
upper limit	1.142

Secondary: Fatigue Assessment Scale - 6 months

End point title	Fatigue Assessment Scale - 6 months

End point description:

End point type	Secondary

End point timeframe:

at 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[14]	250[15]		
Units: Points				
arithmetic mean (standard deviation)	25.9 (± 8.1)	25.4 (± 7.6)		

Notes:

[14] - Please, note that number of subjects that started the arm was 308 (baseline).

[15] - Please, note that number of subjects that started the arm was 285(baseline).

Statistical analyses

No statistical analyses for this end point

Secondary: Montreal Cognitive Assessment (MOCA) - 6 months

End point title	Montreal Cognitive Assessment (MOCA) - 6 months

End point description:

End point type	Secondary

End point timeframe:

Montreal Cognitive Assessment (MOCA) - 6 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242[16]	250[17]		
Units: Points				
arithmetic mean (standard deviation)	23.1 (± 6.18)	23.6 (± 5.45)		

Notes:

[16] - Please, note that number of subjects that started the arm was 308 (baseline).

[17] - Please, note that number of subjects that started the arm was 285(baseline).

Statistical analyses

Statistical analysis title	stepwise multilevel regression analysis

Statistical analysis description:

Model was adjusted for following covariates: treatment group, gender, stroke type, RMI score at randomisation, baseline MoCA score, age, baseline NEADL score, baseline ABILHAND, days between stroke and randomisation.

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.445
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.269
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.959
upper limit	0.419

Secondary: Rivermead Mobility Index (RMI) continuous - 12 months

End point title	Rivermead Mobility Index (RMI) continuous - 12 months

End point description:

End point type	Secondary

End point timeframe:
Rivermead Mobility Index continuous - 12 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[18]	221[19]		
Units: points				
arithmetic mean (standard deviation)	8.7 (± 4.7)	8.5 (± 4.6)		

Notes:
[18] - Please, note that number of subjects that started the arm was 308 (baseline).
[19] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	multilevel linear regression
Statistical analysis description: model was adjusted for the same covariates as per primary endpoint analysis	
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.881

Secondary: Barthel Index at 12 months

End point title	Barthel Index at 12 months
End point description:	

End point type	Secondary
End point timeframe: Barthel Index at 12 months	

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[20]	221[21]		
Units: Points				
arithmetic mean (standard deviation)	14.4 (± 5.4)	14.6 (± 5.1)		

Notes:

[20] - Please, note that number of subjects that started the arm was 308 (baseline).

[21] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	Stepwise multilevel linear regression analysis

Statistical analysis description:

model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline Barthel index, baseline MoCA score, baseline NEADL score and days between stroke and randomisation

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.591
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.042
upper limit	0.594

Secondary: ABILHAND Scale - 12 months

End point title	ABILHAND Scale - 12 months

End point description:

End point type	Secondary

End point timeframe:

ABILHAND Scale - 12 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[22]	221[23]		
Units: Logits				
arithmetic mean (standard deviation)	6.5 (± 10.3)	5.3 (± 9.6)		

Notes:

[22] - Please, note that number of subjects that started the arm was 308 (baseline).

[23] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	multilevel linear regression analysis
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.592
upper limit	0.278

Secondary: Nottingham Extended Activities of Daily Living (NEADL) Scale - 12 months

End point title	Nottingham Extended Activities of Daily Living (NEADL) Scale - 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[24]	221[25]		
Units: Points				
arithmetic mean (standard deviation)	30.4 (± 19.4)	29.8 (± 18.9)		

Notes:

[24] - Please, note that number of subjects that started the arm was 308 (baseline).

[25] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	multilevel linear regression analysis

Statistical analysis description:

model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline NEADL score, baseline MoCA, baseline Barthel index and days between stroke and randomisation

Comparison groups	Co-careldopa v Placebo

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.434
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.564
upper limit	3.636

Secondary: General Health Questionnaire 12 - at 12 months

End point title	General Health Questionnaire 12 - at 12 months

End point description:

End point type	Secondary

End point timeframe:

at 12 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[26]	221[27]		
Units: Points				
arithmetic mean (standard deviation)	14 (± 6.77)	14.4 (± 7.16)		

Notes:

[26] - Please, note that number of subjects that started the arm was 308 (baseline).

[27] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression analysis

Statistical analysis description:

model was adjusted for gender, stroke type, RMI score at randomisation, age, baseline GHQ12 score, baseline NEADL and baseline Barthel index

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.769

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.006
upper limit	0.518

Secondary: Fatigue Assessment Scale - 12 months

End point title	Fatigue Assessment Scale - 12 months

End point description:

End point type	Secondary

End point timeframe:
at 12 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[28]	221[29]		
Units: Points				
arithmetic mean (standard deviation)	24.9 (± 8.3)	24.5 (± 8.2)		

Notes:
[28] - Please, note that number of subjects that started the arm was 308 (baseline).
[29] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

No statistical analyses for this end point

Secondary: Montreal Cognitive Assessment (MOCA) - 12 months

End point title	Montreal Cognitive Assessment (MOCA) - 12 months

End point description:

End point type	Secondary

End point timeframe:
Montreal Cognitive Assessment (MOCA) - 12 months

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[30]	221[31]		
Units: Point				
arithmetic mean (standard deviation)	23.1 (± 5.93)	23.5 (± 5.64)		

Notes:

[30] - Please, note that number of subjects that started the arm was 308 (baseline).

[31] - Please, note that number of subjects that started the arm was 285 (baseline).

Statistical analyses

Statistical analysis title	stepwise multilevel regression analysis

Statistical analysis description:

Model was adjusted for following covariates: treatment group, gender, stroke type, RMI score at randomisation, baseline MoCA score, age, baseline NEADL score, baseline ABILHAND, days between stroke and randomisation.

Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.613
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.949
upper limit	0.561

Secondary: Rivermead Mobility Index (RMI) continuous - 8 weeks

End point title	Rivermead Mobility Index (RMI) continuous - 8 weeks

End point description:

End point type	Secondary

End point timeframe:

at 8 weeks

End point values	Co-careldopa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	261		
Units: points				
arithmetic mean (standard deviation)	6.8 (± 4.2)	7 (± 4.2)		

Statistical analyses

Statistical analysis title	stepwise multilevel linear regression
Statistical analysis description: model was adjusted for the same covariates in model for primary endpoint analysis	
Comparison groups	Co-careldopa v Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.198
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.354
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.894
upper limit	0.186

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Randomisation until 30 days after the last dose of Co-careldopa/placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Co-careldopa

Reporting group description:

Active arm

Reporting group title	Placebo

Reporting group description:

Control arm

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There are no non-serious adverse events recorded for these results. Leeds Institute of Clinical Trials Research is an academic trials unit where full MedDRA coding of non-serious adverse events is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories can not be completed. A summary of non-serious adverse events is available if required.

Serious adverse events	Co-careldopa	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 308 (18.51%)	50 / 285 (17.54%)	
number of deaths (all causes)	22	17	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma	Additional description: Lung cancer with multiple PEs (Pulmonary Embolisms)		
subjects affected / exposed	1 / 308 (0.32%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioma - Brain			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

PV bleed			
subjects affected / exposed	0 / 308 (0.00%)	2 / 285 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 308 (0.32%)	2 / 285 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	10 / 308 (3.25%)	5 / 285 (1.75%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faint, clammy unwell			
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Nausea & dizziness		
subjects affected / exposed	2 / 308 (0.65%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive event			
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid endarterectomy			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Epistaxis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroids			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chest infection			
subjects affected / exposed	5 / 308 (1.62%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 308 (0.97%)	8 / 285 (2.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	Additional description: Exacerbation of COPD		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate decreased	Additional description: acute or chronic		
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Self harm			

subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 308 (0.65%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hallucination	Additional description: Hallucinations (drug induced)		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Fast AF, Heart failure & chest infection		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable	Additional description: Angina		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	2 / 308 (0.65%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter	Additional description: Paroxymal atrial flutter & hypotension		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain	Additional description: Pain - chest/thorax		
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	5 / 308 (1.62%)	5 / 285 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma	Additional description: Right sided Cerebral haemorrhage Left occipital haemorrhage		
subjects affected / exposed	1 / 308 (0.32%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy	Additional description: Post Stroke Epilepsy, epilepsy		
subjects affected / exposed	2 / 308 (0.65%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 308 (0.32%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Numbness	Additional description: Pain and left hand Numbness		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: ?Transient ischaemic attack ? Postural Hypertension		
subjects affected / exposed	0 / 308 (0.00%)	2 / 285 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Falls			

subjects affected / exposed	1 / 308 (0.32%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal attack			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Severe anaemia and low albumin and chest infection.		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea and C. Difficile		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea and vomiting		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Intra-abdominal fluid (free). Pleural effusion. Positive blood cultures.		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Cholecystitis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena	Additional description: Melaena/PR bleed and dehydration		

subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver scan abnormal	Additional description: Liver neoplasm - suspected.		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallstone ileus			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Kidney failure	Additional description: Acute Kidney failure secondary to lower respiratory tract infection/Pneumonia with sepsis		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Fracture	Additional description: Fracture left neck of femur Radial head fracture of right arm, displaced intracapsular fracture of neck of femur, fracture of rich acetabulum.		
subjects affected / exposed	2 / 308 (0.65%)	3 / 285 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Staphylococcus test positive	Additional description: Rigors - increased, stoma output, diagnosed as stpah aureus infection		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 308 (0.97%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 308 (0.65%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess	Additional description: Psoas abscess		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic clonic event	Additional description: Tonic clonic event		

subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Community acquired Pneumonia /Gastroenteritis		
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 308 (0.32%)	2 / 285 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Headache	Additional description: Headache/New onset diabetes		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration	Additional description: Dehydration & mild renal impairment		
subjects affected / exposed	1 / 308 (0.32%)	0 / 285 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Collapse			
subjects affected / exposed	0 / 308 (0.00%)	1 / 285 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Co-careldopa	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 308 (0.00%)	0 / 285 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2010	Protocol version 3.0 dated 9 July 2010 Eligibility criteria updated with the following: •inclusion criteria amended to include patients with 'new' strokes. •Cannot walk 10 metres or more indoors independently •Professionally scored Rivermead Mobility Index score of <7. •Expected to be able to comply with treatment schedule post randomisation (e.g. swallow whole tablets) •Expected to be in hospital for at least their first two doses trial medication •Diagnosis of Parkinson's disease, dementia, severe medical or surgical illness, severe psychosis or glaucoma •Symptomatic orthostatic hypotension •Patients currently participating in other interventional drug or treatment therapy trials Defined end of trial as the date of the last patient's last 8 week follow-up visit for the purpose of safety reporting. Primary endpoint measure clarified to '...as measured by a score of 7 or higher and who also answer 'yes' to item number 7 on the Rivermead Mobility Index'.
25 July 2011	Protocol v4.0 - amended eligibility criteria to include new clinically 'first' diagnosed ischaemic or haemorrhagic stroke in the 2 weeks prior to randomisation. Removed dementia from exclusion criteria and aligned criteria to match Co-careldopa SPC.
20 December 2011	Protocol v5.0 - trial design changed to the following: - to enable participants to receive either Co-careldopa/placebo within 7-28 days post stroke. -to enable co-enrolment for participants taking part in other non-CTIMP/observational trials Consent forms amended to enable an annonymised copy of the CT/MRI scan to be transferred to CTRU. -Sufficient motor therapy defined as at least 20 mins of motor therapy in at least 80% of therapy sessions. Patients complying with medication are those receiving treatment 45-60 mins before therapy begins in at least 80% of therapy sessions.
30 March 2012	Protocol v6.0 - eligibility criteria amended to: -new or recurrent clinically diagnosed ischaemic or haemorrhagic (excluding subarachnoid haemorrhage) stroke within 5 to 42 days prior to randomisation -able to access continuity of rehabilitation treatment following discharge

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported