



Clinical trial results:

A Phase IIa study to assess the safety, tolerability, plasma pharmacokinetics and efficacy of intermittent oral administration of standard levodopa/carbidopa vs. semi-continuous intra-oral administration of levodopa/carbidopa in patients with advanced Parkinson's disease who suffer motor fluctuations.

Summary

EudraCT number	2014-002295-87
Trial protocol	IT
Global end of trial date	07 October 2015

Results information

Result version number	v1 (current)
This version publication date	19 May 2021
First version publication date	19 May 2021
Summary attachment (see zip file)	SynAgileConInfusionPrimaryManuscript (Olanow_et_al-2019-Movement_Disorders.pdf)

Trial information

Trial identification

Sponsor protocol code	LDCD-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	SynAgile Corporation
Sponsor organisation address	3465 N. Pines Way, Suite 104, PMB218, Wilson, United States, 83014
Public contact	Jennifer Harmon, SynAgile, 65 8182 3942, jharmon@synagile.com
Scientific contact	Jennifer Harmon, SynAgile, 65 8182 3942, jharmon@synagile.com
Sponsor organisation name	SynAgile Corporation
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Scientific contact	Jennifer Harmon, SynAgile Corporation, +65 8742 8832, jharmon@synagile.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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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	08 October 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the plasma pharmacokinetics of continuous intra-oral administration of LD/CD vs. intermittent administration of standard oral LD/CD

Protection of trial subjects:

EC approval was obtained prior to the start of the study and all subjects were required to sign the EC approved consent prior to the start of the study. An enrollment authorization committee approved all subjects for participation to ensure all inclusion/exclusion criteria had been met and subjects were suitable for participation. A blinded medical monitor reviewed accumulating data during the conduct of the study to ensure that no safety trends were emerging.

Background therapy:

3Stable doses of levodopa plus/minus other dopaminergic therapy (minimum of 4 weeks for each drug). Subjects were excluded if they were receiving duodopa, apomorphine infusion or DBS.

Evidence for comparator:

Comparator on Day 1 was usual oral L-dopa/carbidopa dose; day 2 was the investigational dose of L-dopa/carbidopa by "continuous" oral administration and Day3 subjects received a single oral L-dopa/carbidopa dose followed by "continuous" oral administration of L-dopa/carbidopa

Actual start date of recruitment	07 July 2014
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	Italy: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
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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)	6
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited directly from one clinical site in Italy from the investigators own patient population

Pre-assignment

Screening details:

Male and female PD subjects of any race aged 35 to 75 years who sign an EC/IRB-approved informed consent. PD diagnosis consistent with UK Brain Bank Criteria. Good response to levodopa with at least 2 hours of wearing off episodes in judgment of investigator Stable doses of levodopa plus/minus other dopaminergic therapy. MMSE>26

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Day 1
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Arm description:

Subjects received their usual oral L-dopa/carbidopa doses

Arm type	Active comparator
Investigational medicinal product name	Standard oral L-dopa/carbidopa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects took their standard oral L-dopa/carbidopa tablets at their individual usual dosage and time

Arm title	Day 2
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Arm description:

Subjects received L-dopa/carbidopa by "continuous" oral administration

Arm type	Experimental
Investigational medicinal product name	Sinemet 25/100 include: 25 mg carbidopa and 100 mg levodopa administered as a dispersion - chopped and mixed in 50 ml of neutral pH water w/out buffer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

At the clinic, investigators will prepare suspensions of LD/CD in distilled or deionized water. Fresh suspensions will be prepared every hour. One tablet of Sinemet 25/100 (each tablet containing 100 mg LD and 25 mg CD) will be chopped up by placing the tablet in a pill cutter and chopping the tablet in half, and mixed or shaken in 50 mL of water in a small glass flask with a stopper. Formulas for the volume to

be taken every 5 minutes were provided to the site as part of the dosing manual.

Arm title	Day 3
Arm description: Subjects received a single dose of oral L-dopa/carbidopa followed by "continuous" oral administration of L-dopa/carbidopa	
Arm type	Experimental
Investigational medicinal product name	Sinemet 25/100 include: 25 mg carbidopa and 100 mg levodopa administered as a dispersion - chopped and mixed in 50 ml of neutral pH water w/out buffer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid, Tablet
Routes of administration	Oral use

Dosage and administration details:

Initial sinemet tablet of 25/100 given as the initial morning dose and then at the clinic, investigators will prepare suspensions of LD/CD in distilled or deionized water. Fresh suspensions will be prepared every hour. One tablet of Sinemet 25/100 (each tablet containing 100 mg LD and 25 mg CD) will be chopped up by placing the tablet in a pill cutter and chopping the tablet in half, and mixed or shaken in 50 mL of water in a small glass flask with a stopper. Formulas for the volume to be taken every 5 minutes were provided to the site as part of the dosing manual.

Number of subjects in period 1	Day 1	Day 2	Day 3
Started	18	18	18
Completed	18	18	18

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	18	18	
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	68		
standard deviation	± 8.9	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	11	11	

End points

End points reporting groups

Reporting group title	Day 1
Reporting group description: Subjects received their usual oral L-dopa/carbidopa doses	
Reporting group title	Day 2
Reporting group description: Subjects received L-dopa/carbidopa by "continuous" oral administration	
Reporting group title	Day 3
Reporting group description: Subjects received a single dose of oral L-dopa/carbidopa followed by "continuous" oral administration of L-dopa/carbidopa	

Primary: Levodopa concentration (ng/ml), fluctuation index (PK set) 4.5-8 hours

End point title	Levodopa concentration (ng/ml), fluctuation index (PK set) 4.5-8 hours
End point description: Fluctuation index is calculated from all concentrations within the time interval difference between Day 2 and Day 3 is tested with t-test.	
End point type	Primary
End point timeframe: 4.5 to 8 hours post dose on Days 2 and 3	

End point values	Day 1	Day 2	Day 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18 ^[1]	18	18	
Units: ng/ml	18	18	18	

Notes:

[1] - Day 1 was not included in the primary endpoint

Statistical analyses

Statistical analysis title	Levodopa concentration (ng/ml), fluctuation index
Statistical analysis description: Fluctuation index is calculated from all concentrations within the time interval difference between Day 2 and Day 3 is tested with t-test	
Comparison groups	Day 2 v Day 3
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.0147 ^[3]
Method	t-test, 2-sided

Notes:

[2] - fluctuation index

[3] - Mean on Day 2 is 1.38, SD of 0.51. On Day 3 mean = 0.99 with SD 0.39

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

From the time of signing informed consent through last study visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Frequency threshold for reporting non-serious adverse events: 1 %

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: A total of 3 non-serious adverse events occurred in 2 subjects. All were determined to be mild in severity and not related. Reported terms are accidental fall, pelvic contusion, and fever.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30653246>