



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 | LDCCD-001 |
|-----------------------|-----------|

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 |
| Sponsor organisation address | 3465 N. Pines Way, Suite 104, PMB 218, Wilson, United States, 83014 |
| Public contact | Jennifer Harmon, SynAgile Corporation, +65 8742 8832, jharmon@synagile.com |
| 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 |
|--|----|

| | |
|--|----|
| 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 |
|----------|---|

| | |
|---|----|
| 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 |
| Arm title | Day 1 |

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 |
|------------------|-------|

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 |
|-----------------------|---------------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

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>