



## Clinical trial results:

### The Effect of Rotigotine on Memory in Idiopathic Parkinson's Disease without Cognitive Impairment

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-000335-17 |
| Trial protocol           | GB             |
| Global end of trial date | 12 June 2015   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 18 June 2016 |
| First version publication date | 18 June 2016 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | MPR001 |
|-----------------------|--------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                                        |
|------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | University Hospitals of North Midlands NHS Trust                                                                       |
| Sponsor organisation address | Newcastle Road, Staffordshire, United Kingdom, ST4 6QG                                                                 |
| Public contact               | Dr Darren Clement, University Hospitals of North Midlands NHS Trust<br>, 0044 01782 675379, Darren.Clement@uhnm.nhs.uk |
| Scientific contact           | Dr Darren Clement, University Hospitals of North Midlands NHS Trust<br>, 0044 01782 675379, Darren.Clement@uhnm.nhs.uk |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 12 June 2015 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 12 June 2015 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 12 June 2015 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

This is not a hypothesis testing trial, but an acceptability and feasibility trial. The primary objectives are (i) to obtain estimates of memory performance which will inform a power calculation which will inform a larger, multi-centered, fully powered investigation, data collected during ON and OFF research sessions;

(ii) management of symptoms during washout period, assessed using a semi-structured interview administered at the end of each patient-participant's involvement in the trial.

The study also performed the same memory assessments on healthy volunteers (no study drug administered).

Protection of trial subjects:

This trial did not involve changing the patient-participants' prescribed medication (drug or dose). The interventions included a memory/neuropsychological testing session conducted both following a medication withdrawal period (OFF-medication session) and on medications (ON -medication session). Each patient-participant was telephoned by a research nurse within two working days of their OFF-medication session and also participants had access to a 24 hour contact telephone number should concerns arise.

Background therapy:

Participants were permitted a range of Parkinson's medications :

A) PD patients currently medicated with rotigotine transdermal patch, dose range 2-16mg per 24 hours (with/without a controlled-release preparation of l-dopa, with/without a monoamine oxidase B inhibitor such as rasagiline/Azilect (0.5-1mg per 24 hours) or selegiline/ Eldepryl (5mg -12mg per 24 hours), Zelapar (1.25mg – 2.5mg per day).

B) PD patients currently medicated with a controlled-release l-dopa preparation, dose range 150-1,200mg/per 24 hours (with/without a monoamine oxidase B inhibitor such as rasagiline/Azilect (0.5-1mg per 24 hours) or selegiline/ Eldepryl (5mg -12mg per 24 hours), Zelapar (1.25mg – 2.5mg per day).

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 13 April 2015 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Worldwide total number of subjects   | 14                 |
| EEA total number of subjects         | 14                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                      | 1  |
| From 65 to 84 years                       | 13 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patient participants with Parkinson's Disease were recruited from the University Hospitals of North Midlands NHS Trust.

Healthy volunteers (who did not receive any study drugs) who underwent the same regimen of memory testing were recruited at Keele University (a non-NHS Site).

### Pre-assignment

Screening details:

For Parkinson's patients : Screening visit/questionnaires: Review of inclusion/exclusion criteria, medical history and current medication, Functional assessment of mental capacity by Investigator, informed consent, mini-mental state exam, physical exam, vital signs, PD symptom assessment, Hospital Anxiety and Depression scale, subjective mood.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 14 |
| Number of subjects completed | 13 |

### Pre-assignment subject non-completion reasons

|                            |                                                     |
|----------------------------|-----------------------------------------------------|
| Reason: Number of subjects | Screen fail: Had a family history of Parkinson's: 1 |
|----------------------------|-----------------------------------------------------|

### Period 1

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

Blinding implementation details:

Keele researcher was blinded to the Parkinson's participants medication but not to the ON or OFF medication status.

### Arms

|                              |                                   |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes                               |
| Arm title                    | Parkinson's : Rotigotine patients |

Arm description:

Patient medicated with rotigotine transdermal patch, dose range 2-16mg per 24 hours (with or without a controlled-release preparation of levodopa, with or without a monoamine oxidase B inhibitor such as rasagiline/Azilect or selegiline/ Eldepryl, Zelapar).

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Rotigotine                   |
| Investigational medicinal product name | Rotigotine transdermal patch |
| Investigational medicinal product code | ATC code: N04BC09            |
| Other name                             |                              |
| Pharmaceutical forms                   | Transdermal patch            |
| Routes of administration               | Transdermal use              |

Dosage and administration details:

Dose range 2-16mg per 24 hours

For the "ON" session, medication to be taken as usual

For the "OFF" session: Patch to be removed at 9am the day prior to testing. Patch to be resumed after the testing session.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Levodopa + Benserazide |
| Investigational medicinal product code |                        |
| Other name                             | e.g. Madopar           |

|                          |                                                                    |
|--------------------------|--------------------------------------------------------------------|
| Pharmaceutical forms     | Capsule, hard, Dispersible tablet, Prolonged-release capsule, hard |
| Routes of administration | Oral use                                                           |

Dosage and administration details:

Levodopa dose range 150-1,200mg / 24 hours. Combination of controlled release and immediate release was permitted.

For the "ON" session, medication to be taken as usual

For the "OFF" session: L-dopa withdrawn 12 hours (i.e. overnight) before the OFF -medication session

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Investigational medicinal product name | Levodopa + carbidopa             |
| Investigational medicinal product code |                                  |
| Other name                             | e.g. Sinemet                     |
| Pharmaceutical forms                   | Prolonged-release tablet, Tablet |
| Routes of administration               | Oral use                         |

Dosage and administration details:

Levodopa dose range 150-1,200mg / 24 hours. Combination of controlled release and immediate release was permitted.

For the "ON" session, medication to be taken as usual

For the "OFF" session: L-dopa withdrawn 12 hours (i.e. overnight) before the OFF -medication session

The following combinations were permitted:

Sinemet 12.5mg/50mg, (12.5mg anhydrous carbidopa + 50mg levodopa),

Sinemet 10mg/100mg (10mg anhydrous carbidopa + 100mg levodopa),

Simemet Plus (25mg/100mg (25mg anhydrous carbidopa + 100mg levodopa),

Sinemet 25mg/250mg (25mg anhydrous carbidopa + 250mg levodopa)

CR (50mg anhydrous carbidopa + 200mg levodopa)

Prolonged Release tablets and Half Sinemet CR (25mg anhydrous carbidopa+100mg levodopa)

|                                        |                                                          |
|----------------------------------------|----------------------------------------------------------|
| Investigational medicinal product name | Selegiline hydrochloride (monoamine oxidase B inhibitor) |
| Investigational medicinal product code |                                                          |
| Other name                             | e.g. Elderpryl or Zelapar                                |
| Pharmaceutical forms                   | Oral lyophilisate, Tablet                                |
| Routes of administration               | Oral use, Sublingual use                                 |

Dosage and administration details:

Tablet: 12mg/ 24 hours permitted

Oral Lyophilisate: 1.25-2.5 mg / 24 hours

For the "ON" session, medication to be taken as usual

For the "OFF" session: withdrawn 12 hours (i.e. overnight) before the OFF -medication session

|                                        |                              |
|----------------------------------------|------------------------------|
| Investigational medicinal product name | Rasagiline (MAO-B inhibitor) |
| Investigational medicinal product code |                              |
| Other name                             | e.g. Azilect                 |
| Pharmaceutical forms                   | Tablet                       |
| Routes of administration               | Oral use                     |

Dosage and administration details:

Dose range 0.5 - 1mg / 24 hours.

For the "ON" session, medication to be taken as usual

For the "OFF" session: MOA-B Inhibitor withdrawn 12 hours (i.e. overnight) before the OFF -medication session

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Parkinson's L-Dopa patients |
|------------------|-----------------------------|

Arm description:

Patient medicated with controlled-release preparation of levodopa (in combination with an immediate release formulation was permitted), with or without a monoamine oxidase B inhibitor such as rasagiline/Azilect or selegiline/ Eldepryl, Zelapar).

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                                                                    |
|----------------------------------------|--------------------------------------------------------------------|
| Investigational medicinal product name | Levodopa + Benserazide                                             |
| Investigational medicinal product code |                                                                    |
| Other name                             | e.g. Madopar                                                       |
| Pharmaceutical forms                   | Capsule, hard, Dispersible tablet, Prolonged-release capsule, hard |
| Routes of administration               | Oral use                                                           |

Dosage and administration details:

Levodopa dose range 150-1,200mg / 24 hours. Combination of controlled release and immediate release was permitted.

For the "ON" session, medication to be taken as usual

For the "OFF" session: L-dopa withdrawn 12 hours (i.e. overnight) before the OFF -medication session

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Investigational medicinal product name | Levodopa + carbidopa             |
| Investigational medicinal product code |                                  |
| Other name                             | e.g. Sinemet                     |
| Pharmaceutical forms                   | Prolonged-release tablet, Tablet |
| Routes of administration               | Oral use                         |

Dosage and administration details:

Levodopa dose range 150-1,200mg / 24 hours. Combination of controlled release and immediate release was permitted.

For the "ON" session, medication to be taken as usual

For the "OFF" session: L-dopa withdrawn 12 hours (i.e. overnight) before the OFF -medication session

The following combinations were permitted:

Sinemet 12.5mg/50mg, (12.5mg anhydrous carbidopa +50mg levodopa),

Sinemet 10mg/100mg (10mg anhydrous carbidopa +100mg levodopa),

Simemet Plus (25mg/100mg (25mg anhydrous carbidopa + 100mg levodopa),

Sinemet 25mg/250mg (25mg anhydrous carbidopa + 250mg levodopa)

CR (50mg anhydrous carbidopa +200mg levodopa)

Prolonged Release tablets and Half Sinemet CR (25mg anhydrous carbidopa+100mg levodopa)

|                                        |                                                          |
|----------------------------------------|----------------------------------------------------------|
| Investigational medicinal product name | Selegiline hydrochloride (monoamine oxidase B inhibitor) |
| Investigational medicinal product code |                                                          |
| Other name                             | e.g. Elderpryl or Zelapar                                |
| Pharmaceutical forms                   | Oral lyophilisate, Tablet                                |
| Routes of administration               | Oral use, Sublingual use                                 |

Dosage and administration details:

Tablet: 5mg to 12mg/ 24 hours permitted

Oral Lyophilisate: 1.25-2.5 mg / 24 hours

For the "ON" session, medication to be taken as usual

For the "OFF" session: withdrawn 12 hours (i.e. overnight) before the OFF -medication session

|                                        |                              |
|----------------------------------------|------------------------------|
| Investigational medicinal product name | Rasagiline (MAO-B inhibitor) |
| Investigational medicinal product code |                              |
| Other name                             | e.g. Azilect                 |
| Pharmaceutical forms                   | Tablet                       |
| Routes of administration               | Oral use                     |

Dosage and administration details:

Dose range 0.5 - 1mg / 24 hours.

For the "ON" session, medication to be taken as usual

For the "OFF" session: MOA-B Inhibitor withdrawn 12 hours (i.e. overnight) before the OFF -medication session

|                                                                               |                         |
|-------------------------------------------------------------------------------|-------------------------|
| <b>Arm title</b>                                                              | Healthy Volunteers      |
| Arm description:                                                              |                         |
| This arm underwent memory assessments only. No study drugs were administered. |                         |
| Arm type                                                                      | Memory assessments only |
| No investigational medicinal product assigned in this arm                     |                         |

Notes:

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

Justification: Keele researcher was blinded to the Parkinson's participants medication but not to the ON or OFF medication status. There was no blinding for the healthy volunteers.

| Number of subjects in period<br>1[2] | Parkinson's :<br>Rotigotine patients | Parkinson's L-Dopa<br>patients | Healthy Volunteers |
|--------------------------------------|--------------------------------------|--------------------------------|--------------------|
|                                      |                                      |                                |                    |
| Started                              | 1                                    | 2                              | 10                 |
| Overall Trial                        | 1                                    | 2                              | 10                 |
| Completed                            | 1                                    | 1                              | 10                 |
| Not completed                        | 0                                    | 1                              | 0                  |
| Unable to schedule memory session    | -                                    | 1                              | -                  |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 14 participants were enrolled. One patient did not meet the inclusion / exclusion criteria at the screening visit and therefore had to be withdrawn. One participant could not schedule a memory testing session with the Keele researcher prior to the researcher's end of contract and had to be withdrawn.

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                  |                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                            | Parkinson's : Rotigotine patients |
| Reporting group description:                                                                                                                                                                                                                                     |                                   |
| Patient medicated with rotigotine transdermal patch, dose range 2-16mg per 24 hours (with or without a controlled-release preparation of levodopa, with or without a monoamine oxidase B inhibitor such as rasagiline/Azilect or selegiline/ Eldepryl, Zelapar). |                                   |
| Reporting group title                                                                                                                                                                                                                                            | Parkinson's L-Dopa patients       |
| Reporting group description:                                                                                                                                                                                                                                     |                                   |
| Patient medicated with controlled-release preparation of levodopa (in combination with an immediate release formulation was permitted), with or without a monoamine oxidase B inhibitor such as rasagiline/Azilect or selegiline/ Eldepryl, Zelapar).            |                                   |
| Reporting group title                                                                                                                                                                                                                                            | Healthy Volunteers                |
| Reporting group description:                                                                                                                                                                                                                                     |                                   |
| This arm underwent memory assessments only. No study drugs were administered.                                                                                                                                                                                    |                                   |

| Reporting group values | Parkinson's : Rotigotine patients | Parkinson's L-Dopa patients | Healthy Volunteers |
|------------------------|-----------------------------------|-----------------------------|--------------------|
| Number of subjects     | 1                                 | 2                           | 10                 |
| Age categorical        |                                   |                             |                    |
| Age of participants    |                                   |                             |                    |
| Units: Subjects        |                                   |                             |                    |
| Adults (18-64 years)   | 0                                 | 0                           | 1                  |
| From 65-84 years       | 1                                 | 2                           | 9                  |
| 85 years and over      | 0                                 | 0                           | 0                  |
| Age continuous         |                                   |                             |                    |
| Units: years           |                                   |                             |                    |
| arithmetic mean        | 77.4                              | 73.5                        | 70.1               |
| standard deviation     | ± 0                               | ± 7.7                       | ± 5.1              |
| Gender categorical     |                                   |                             |                    |
| Gender of participants |                                   |                             |                    |
| Units: Subjects        |                                   |                             |                    |
| Female                 | 0                                 | 0                           | 5                  |
| Male                   | 1                                 | 2                           | 5                  |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 13    |  |  |
| Age categorical        |       |  |  |
| Age of participants    |       |  |  |
| Units: Subjects        |       |  |  |
| Adults (18-64 years)   | 1     |  |  |
| From 65-84 years       | 12    |  |  |
| 85 years and over      | 0     |  |  |
| Age continuous         |       |  |  |
| Units: years           |       |  |  |
| arithmetic mean        |       |  |  |
| standard deviation     | -     |  |  |

|                        |   |  |  |
|------------------------|---|--|--|
| Gender categorical     |   |  |  |
| Gender of participants |   |  |  |
| Units: Subjects        |   |  |  |
| Female                 | 5 |  |  |
| Male                   | 8 |  |  |

### Subject analysis sets

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Memory Assessments (PD patients) |
| Subject analysis set type  | Full analysis                    |

Subject analysis set description:

This was a feasibility study. Due to the small sample size, no formal comparison of memory assessments was undertaken.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | End of Study Interviews |
| Subject analysis set type  | Full analysis           |

Subject analysis set description:

End of study interviews for the two Parkinson's patients.

|                            |                                         |
|----------------------------|-----------------------------------------|
| Subject analysis set title | Memory Assessments (Healthy volunteers) |
| Subject analysis set type  | Full analysis                           |

Subject analysis set description:

Healthy control data was collected from 10 volunteers which was smaller than the 25 target, but sufficient for analysis.

They completed the same neurological test battery with the purpose of providing normal / baseline performance data, however the small number of participants recruited to the rotigotine / levodopa arms precluded any meaningful statistical comparison of data

| Reporting group values | Memory Assessments (PD patients) | End of Study Interviews | Memory Assessments (Healthy volunteers) |
|------------------------|----------------------------------|-------------------------|-----------------------------------------|
| Number of subjects     | 2                                | 2                       | 10                                      |
| Age categorical        |                                  |                         |                                         |
| Age of participants    |                                  |                         |                                         |
| Units: Subjects        |                                  |                         |                                         |
| Adults (18-64 years)   |                                  |                         | 1                                       |
| From 65-84 years       | 2                                | 2                       | 9                                       |
| 85 years and over      |                                  |                         |                                         |
| Age continuous         |                                  |                         |                                         |
| Units: years           |                                  |                         |                                         |
| arithmetic mean        | 72.7                             | 72.7                    | 70.1                                    |
| standard deviation     | ± 6.6                            | ± 6.6                   | ± 5.1                                   |
| Gender categorical     |                                  |                         |                                         |
| Gender of participants |                                  |                         |                                         |
| Units: Subjects        |                                  |                         |                                         |
| Female                 | 0                                | 0                       | 5                                       |
| Male                   | 2                                | 2                       | 5                                       |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                             | Parkinson's : Rotigotine patients       |
| Reporting group description:<br>Patient medicated with rotigotine transdermal patch, dose range 2-16mg per 24 hours (with or without a controlled-release preparation of levodopa, with or without a monoamine oxidase B inhibitor such as rasagiline/Azilect or selegiline/ Eldepryl, Zelapar).                                                                                                                                  |                                         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                             | Parkinson's L-Dopa patients             |
| Reporting group description:<br>Patient medicated with controlled-release preparation of levodopa (in combination with an immediate release formulation was permitted), with or without a monoamine oxidase B inhibitor such as rasagiline/Azilect or selegiline/ Eldepryl, Zelapar).                                                                                                                                             |                                         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                             | Healthy Volunteers                      |
| Reporting group description:<br>This arm underwent memory assessments only. No study drugs were administered.                                                                                                                                                                                                                                                                                                                     |                                         |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                        | Memory Assessments (PD patients)        |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                         | Full analysis                           |
| Subject analysis set description:<br>This was a feasibility study. Due to the small sample size, no formal comparison of memory assessments was undertaken.                                                                                                                                                                                                                                                                       |                                         |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                        | End of Study Interviews                 |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                         | Full analysis                           |
| Subject analysis set description:<br>End of study interviews for the two Parkinson's patients.                                                                                                                                                                                                                                                                                                                                    |                                         |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                        | Memory Assessments (Healthy volunteers) |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                         | Full analysis                           |
| Subject analysis set description:<br>Healthy control data was collected from 10 volunteers which was smaller than the 25 target, but sufficient for analysis.<br>They completed the same neurological test battery with the purpose of providing normal / baseline performance data, however the small number of participants recruited to the rotigotine / levodopa arms precluded any meaningful statistical comparison of data |                                         |

### Primary: Estimates of memory performance

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Estimates of memory performance <sup>[1]</sup> |
| End point description:<br>For Parkinson's Patients, memory assessments performed for the ON research session involved the patient taking medications as usual. For the OFF session, medication was delayed prior to the memory recollection research session. Medication was resumed following completion of the memory assessments.<br><br>For the healthy volunteers, these underwent two memory assessments (called "blue" and "green" to mirror the Parkinson's patients assessments. The healthy volunteers underwent no change in medications. |                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Primary                                        |
| End point timeframe:<br>This was a feasibility study. Primary endpoint was to obtain estimates of memory performance which will inform a power calculation, data collected during ON and OFF research sessions                                                                                                                                                                                                                                                                                                                                       |                                                |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: This was a feasibility study. There was insufficient recruitment to provide estimates to inform a power calculation.                                                                                                                                                                                                                                 |                                                |

| End point values            | Parkinson's : Rotigotine patients | Parkinson's L-Dopa patients | Healthy Volunteers | Memory Assessments (PD patients) |
|-----------------------------|-----------------------------------|-----------------------------|--------------------|----------------------------------|
| Subject group type          | Reporting group                   | Reporting group             | Reporting group    | Subject analysis set             |
| Number of subjects analysed | 0 <sup>[2]</sup>                  | 0 <sup>[3]</sup>            | 0 <sup>[4]</sup>   | 0 <sup>[5]</sup>                 |
| Units: Memory recall        |                                   |                             |                    |                                  |
| number (not applicable)     |                                   |                             |                    |                                  |

Notes:

[2] - This was a feasibility study. There was insufficient recruitment for analysis.

[3] - This was a feasibility study. There was insufficient recruitment for analysis.

[4] - This was a feasibility study. There was insufficient recruitment for analysis.

[5] - This was a feasibility study. There was insufficient recruitment for analysis.

| End point values            | End of Study Interviews | Memory Assessments (Healthy volunteers) |  |  |
|-----------------------------|-------------------------|-----------------------------------------|--|--|
| Subject group type          | Subject analysis set    | Subject analysis set                    |  |  |
| Number of subjects analysed | 0 <sup>[6]</sup>        | 0 <sup>[7]</sup>                        |  |  |
| Units: Memory recall        |                         |                                         |  |  |
| number (not applicable)     |                         |                                         |  |  |

Notes:

[6] - End of study interviews provided valuable data for the feasibility study

[7] - This was a feasibility study. There was insufficient recruitment for analysis.

## Statistical analyses

No statistical analyses for this end point

## Primary: Semi-structured interview

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | Semi-structured interview <sup>[8]</sup> |
|-----------------|------------------------------------------|

End point description:

Semi structured interview for Parkinson's patients at the end of the trial.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Primary End point: management of symptoms during washout period, assessed using a semi-structured interview administered at the end of each patient-participant's involvement in the trial.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The healthy volunteers did not require an end of study interview for this feasibility study.

| End point values            | Parkinson's : Rotigotine patients | Parkinson's L-Dopa patients | End of Study Interviews |  |
|-----------------------------|-----------------------------------|-----------------------------|-------------------------|--|
| Subject group type          | Reporting group                   | Reporting group             | Subject analysis set    |  |
| Number of subjects analysed | 1 <sup>[9]</sup>                  | 1 <sup>[10]</sup>           | 2 <sup>[11]</sup>       |  |
| Units: N/A                  | 1                                 | 1                           | 2                       |  |

Notes:

[9] - One patient from this group has a semi-structured interview

[10] - One patient from this group has a semi-structured interview

[11] - Two participants underwent semi-structured interviews

## Statistical analyses

|                                         |                                                                                              |
|-----------------------------------------|----------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | End of Study Interviews                                                                      |
| Statistical analysis description:       |                                                                                              |
| Qualitative data only                   |                                                                                              |
| Comparison groups                       | Parkinson's : Rotigotine patients v Parkinson's L-Dopa patients<br>v End of Study Interviews |
| Number of subjects included in analysis | 4                                                                                            |
| Analysis specification                  | Post-hoc                                                                                     |
| Analysis type                           | other <sup>[12]</sup>                                                                        |
| P-value                                 | = 0 <sup>[13]</sup>                                                                          |
| Method                                  | NOT DONE                                                                                     |

Notes:

[12] - Qualitative data: Interviews identified the following main themes:

1-Trial contact: Participants were happy with the approach

2-Trial information: Felt it was interesting but possibly too much jargon

3-Reasons for taking part: In general: altruism and making a contribution to a break through; specifically to learn more about their own medication and its effects.

4-Experience of taking part: Participants enjoyed the assessments and it wasn't a burden

This was a feasibility study only.

[13] - NOTE: No P-value calculated "0" entered above to fulfil validation report only. Please ignore value.

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Adverse events were collected from consent to the last study visit. Participants were telephoned by the research nurses after the last visit to collect any adverse event information.

Adverse event reporting additional description:

Worsening of Parkinson's symptoms during the "OFF" medication session were not considered to be adverse events as they were expected during an unmedicated state.

No adverse events were reported for this trial.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |            |
|--------------------|------------|
| Dictionary name    | WHO ICD-10 |
| Dictionary version | 2016       |

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description:

Adverse events for overall trial (note no adverse events were reported)

| Serious adverse events                            | Overall trial |  |  |
|---------------------------------------------------|---------------|--|--|
| Total subjects affected by serious adverse events |               |  |  |
| subjects affected / exposed                       | 0 / 2 (0.00%) |  |  |
| number of deaths (all causes)                     | 0             |  |  |
| number of deaths resulting from adverse events    | 0             |  |  |

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

| Non-serious adverse events                            | Overall trial |  |  |
|-------------------------------------------------------|---------------|--|--|
| Total subjects affected by non-serious adverse events |               |  |  |
| subjects affected / exposed                           | 0 / 2 (0.00%) |  |  |

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 were only two Parkinson's participants who completed the trial (and 10 healthy volunteers in the healthy volunteer arm). There were no adverse events reported.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 January 2015  | Administrative amendment to the MHRA. Change in sponsor name from University Hospitals of North Staffordshire NHS trust to University Hospitals of North Midlands NHS Trust.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 13 February 2015 | <p>Change in recruiting Trust Name from University Hospitals of North Staffordshire to University Hospitals of North Midlands NHS Trust (Note: MHRA administrative change Amendment 01)</p> <p>Patient who also take immediate release preparation L-Dopa, in addition to a controlled released preparation as part of their Parkinson's treatment are now eligible to participate.</p> <p>Added English as a first language in to the inclusion of the healthy volunteer group to match up in line with the patient-participant inclusion criteria.</p> <p>Current or planned participation in another research trial changed to another drug trial to include those patients on other observational, non interventional research studies.</p> <p>Treatment for Cancer has been changed to Treatment for Cancer (excluding Basal Cell Carcinoma).</p> <p>Hypotension has been changed to Clinically significant Hypotension</p> <p>Major Head injury has been changed to Major Head injury in the last twelve months (Healthy volunteers)</p> <p>Changes to Contraindicated Treatments</p> <p>Anticholinergics have been changed to centrally acting anticholinergic (e.g Orphenadrine, Trihexyphenidyl Procyclidine)</p> <p>Added the statement: Note: Anticholinergics used the treatment of asthma that do not cross the blood brain barrier (e.g Atrovent) are permitted.</p> <p>Follow up</p> <p>Each patient Participant will now be telephoned by a research nurse within two working days of their OFF-medication session Patient-participants will also be telephone within 7-28 days of completing their participation in the trial to discuss any adverse events that they experience during the trial.</p> <p>Updated reference safety information and formulations and dosages of each IMP</p> <p>Added instructions on dispensing, modification of trial treatment, overdose management, accountability, compliance and destruction.</p> <p>Adverse Events</p> <p>Added worsening of Parkinson's symptoms during the 'OFF' session are not to be recorded as adverse events as this is expected during the patient's unmediated state</p> |
| 23 March 2015    | <p>MHRA approved 23-Mar-2015</p> <p>Ethics approved 24-Mar-2015</p> <p>For the MHRA, this amendment includes all changes specified in previous amendment plus the following:</p> <p>Levodopa maximum dose amended from 1000mg to 1200mg/24 hours</p> <p>Clarified that Rotigotine patch to be removed at 9:00am the day prior to the off testing session.</p> <p>Recent Head Injury added to exclusion criteria (patient-participants)</p> <p>End of study interviews to include first 3 levodopa and first 3 rotigotine patients</p> <p>Epworth sleepiness scale added to ON session assessments</p> <p>Updated HADS, Mini-mental and submitted Mental capacity Act for completeness</p> <p>Updates to other study documents in line with the above.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 17 April 2015    | Added Keele as a NON-NHS Site for the healthy volunteer assessments.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

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

|                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| It is important to note that at this stage in the program of research there is still no firm evidence that dopaminergic medication affects memory. Therefore people with Parkinson's should NOT change their medication based on this feasibility study. |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes: