



Clinical trial results:

A randomised, double blind, placebo controlled, single centre, 60 week trial of Exenatide once weekly for the treatment of moderate severity Parkinson's disease.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-003363-64 |
| Trial protocol | GB |
| Global end of trial date | 12 May 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 22 March 2018 |
| First version publication date | 22 March 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 13/0384 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|------------------------------|
| ISRCTN number | ISRCTN75891427 |
| ClinicalTrials.gov id (NCT number) | NCT01971242 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | FoxTrialFinder: Exenatide-pd |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Comprehensive Clinical Trials Unit at UCL |
| Sponsor organisation address | Institute of Clinical Trials and Methodology, 90 High Holborn , London, United Kingdom, WC1V 6LJ |
| Public contact | CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk |
| Scientific contact | CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.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 | 27 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 April 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To generate further data to explore whether 48 weeks exposure to Exenatide has an advantage over placebo based on a standard validated assessment of Parkinson's disease severity (the MDS UPDRS part 3 motor subscale). This was measured during the "practically defined OFF medication state" i.e. after patients had withheld their conventional PD medication overnight. The hypothesis was that Exenatide would be associated with reduced MDS UPDRS part 3 scores at the study end.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, the EU Tissue and Cells Directives 2004/23/EC, 2006 17/EC and 2006/86/EC, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

Protocol pre-defined reasons for a temporary halt of trial medication were in place in the event of participants experiencing abdominal pain consistent with a clinical diagnosis of pancreatitis or excessive/undesirable weight loss (>10% of body weight during a 12 week interval).

Protocol pre-defined reasons for discontinuation of trial medication were in place in the event of participants experiencing any of the following: diagnosis of acute pancreatitis; an elevation in serum Amylase (>50% above baseline); developing clinical suspicion of thyroid malignancy; accelerated disease progression (defined as greater than 50% (and absolute value of 20 points) decline in MDS UPDRS part 3 motor sub-score from baseline in both the ON medication and the practically defined OFF medication states).

Broader protocol pre-defined reasons for discontinuation of trial medication: unacceptable treatment toxicity or adverse event; inter-current illness that prevented further treatment; any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment. All participants could choose to discontinue trial treatment at any time, without giving a reason, without penalty or loss of benefits to which they would otherwise be entitled.

Investigation and treatment of adverse events were as per NHS standard of care.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 15 April 2014 |
| 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: 62 |
|--------------------------------------|--------------------|

| | |
|------------------------------------|----|
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 62 |

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) | 41 |
| From 65 to 84 years | 21 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients with moderate Parkinson's disease were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. The trial was done at the Leonard Wolfson Experimental Neuroscience Centre (London, UK).

Pre-assignment

Screening details:

Inclusion: Patients aged 25–75 years, idiopathic Parkinson's disease as measured by Queen Square Brain Bank criteria, on dopaminergic treatment with wearing-off effects, judged able to administer the trial drug, and at Hoehn and Yahr stage 2.5 or less when on treatment. Exclusion: concurrent dementia (MATTIS DRS<120), BMI<18.5 and diabetes.

Pre-assignment period milestones

| | |
|------------------------------|-------------------|
| Number of subjects started | 68 ^[1] |
| Number of subjects completed | 62 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Physician decision: 1 |
| Reason: Number of subjects | Consent withdrawn by subject: 3 |
| Reason: Number of subjects | Protocol deviation: 2 |

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: The number of subjects reported in the pre-assignment period are the numbers who were screened for the trial but not randomised into the trial. The worldwide number enrolled is the number of patients who were eligible, consented and randomised into the trial.

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Main Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Blinding implementation details:

The trial statistician generated and uploaded unique three-digit identifiers for every active and placebo drug kit to the randomisation service to allow allocation of masked study drug kits (sufficient for 12 weeks) at randomisation and follow-up visits by assessing clinicians. The randomisation service then provided the relevant kit numbers that were to be dispensed to the patient from the hospital pharmacy.

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Exenatide |

Arm description:

Exenatide extended release 2mg subcutaneous injection (Bydureon) once weekly for 48 weeks.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Exenatide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Each dose of Exenatide extended release is supplied as a vial containing the Exenatide powder and an inactive ingredient called polylactide-co-glycolide and sucrose. This is supplied together with diluent (sterile water containing carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and sodium chloride) to allow reconstitution of the powder in solution for subcutaneous administration by the patient on a weekly basis. 2mg once weekly for 48 weeks.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Each dose of Placebo - Exenatide extended release is supplied as a vial containing a powder together with diluent to allow reconstitution of solution for subcutaneous administration by the patient on a weekly basis.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Each dose of Placebo- Exenatide extended release is supplied as a vial containing a powder together with diluent to allow reconstitution of solution for subcutaneous administration by the patient on a weekly basis. Once weekly for 48 weeks.

| Number of subjects in period 1 | Exenatide | Placebo |
|---------------------------------------|-----------|---------|
| Started | 32 | 30 |
| Completed | 31 | 29 |
| Not completed | 1 | 1 |
| Consent withdrawn by subject | - | 1 |
| Adverse event, non-fatal | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | Exenatide |
| Reporting group description: Exenatide extended release 2mg subcutaneous injection (Bydureon) once weekly for 48 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Each dose of Placebo - Exenatide extended release is supplied as a vial containing a powder together with diluent to allow reconstitution of solution for subcutaneous administration by the patient on a weekly basis. | |

| Reporting group values | Exenatide | Placebo | Total |
|-----------------------------------|-----------|---------|-------|
| Number of subjects | 32 | 30 | 62 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 18 | 23 | 41 |
| From 65-84 years | 14 | 7 | 21 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.9 | 58.3 | |
| standard deviation | ± 8.2 | ± 8.3 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 7 | 16 |
| Male | 23 | 23 | 46 |
| Hoehn & Yahr | | | |
| Units: Subjects | | | |
| Stage 1.0 - 2.0 | 30 | 30 | 60 |
| Stage 2.5 | 2 | 0 | 2 |
| Age at Diagnosis | | | |
| Units: Years | | | |
| arithmetic mean | 56.2 | 52.5 | |
| standard deviation | ± 7.9 | ± 7.8 | - |
| Duration of diagnosis at baseline | | | |
| Units: Years | | | |
| arithmetic mean | 6.3 | 6.5 | |
| standard deviation | ± 3.3 | ± 3.4 | - |
| Levodopa equivalent dose | | | |
| Units: mg | | | |
| arithmetic mean | 760 | 816.8 | |
| standard deviation | ± 268.4 | ± 203.4 | - |
| MDS UPDRS part 3 Off medication | | | |
| Units: unit(s) | | | |
| arithmetic mean | 32.8 | 27.1 | |
| standard deviation | ± 9.7 | ± 10.3 | - |
| MDS UPDRS Part 1 On medication | | | |
| Units: unit(s) | | | |
| arithmetic mean | 9.8 | 9.2 | |

| | | | |
|---|----------------|----------------|---|
| standard deviation | ± 4.8 | ± 3.8 | - |
| MDS UPDRS part 2 On medication Units: unit(s) arithmetic mean standard deviation | 12.5 ± 6.7 | 10.7 ± 5.3 | - |
| MDS UPDRS part 3 On medication Units: unit(s) arithmetic mean standard deviation | 19.4 ± 8.4 | 14.4 ± 8.2 | - |
| MDS UPDRS part 4 On medication Units: unit(s) arithmetic mean standard deviation | 4.7 ± 3.1 | 5.3 ± 3.0 | - |
| MATTIS Dementia Rating scale Units: unit(s) arithmetic mean standard deviation | 138.0 ± 5.0 | 139.8 ± 3.7 | - |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Exenatide |
| Reporting group description: Exenatide extended release 2mg subcutaneous injection (Bydureon) once weekly for 48 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Each dose of Placebo - Exenatide extended release is supplied as a vial containing a powder together with diluent to allow reconstitution of solution for subcutaneous administration by the patient on a weekly basis. | |

Primary: Change from baseline in MDS UPDRS part 3 Off medication at 60 weeks

| | |
|--|---|
| End point title | Change from baseline in MDS UPDRS part 3 Off medication at 60 weeks |
| End point description: The primary endpoint measure for this trial is the MDS UPDRS (part 3) motor sub-score in the practically defined OFF medication state at 60 weeks. | |
| End point type | Primary |
| End point timeframe: At 60 weeks from randomisation | |

| End point values | Exenatide | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: units | | | | |
| arithmetic mean (standard deviation) | 31.9 (\pm 12.0) | 29.2 (\pm 12.0) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Primary outcome analysis |
| Statistical analysis description: We used an analysis of covariance (ANCOVA) model to estimate the difference in MDS UPDRS part 3 subscore between treatments (Exenatide - placebo) at 60 weeks together with a two-sided 95% confidence interval, adjusting for the Hoehn and Yahr score and baseline MDS UPDRS scores which were included as covariates. | |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0318 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -3.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.7 |
| upper limit | -0.3 |

Secondary: Change from baseline in MDS UPDRS part 3 Off medication at 48 weeks

| | |
|---|---|
| End point title | Change from baseline in MDS UPDRS part 3 Off medication at 48 weeks |
| End point description: Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 Motor Examination subsection score. | |
| End point type | Secondary |
| End point timeframe: At 48 weeks post randomisation | |

| End point values | Exenatide | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 29 | | |
| Units: units | | | | |
| arithmetic mean (standard deviation) | 30.2 (\pm 11.1) | 28.8 (\pm 10.8) | | |

Statistical analyses

| | |
|--|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Statistical analysis description: For secondary outcomes, the differences between the two groups were summarised using estimates and confidence intervals, using the ANCOVA approach. | |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0026 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -4.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.1 |
| upper limit | -1.6 |

Secondary: Change from baseline in MDS UPDRS part 1 On medication at 60 weeks

| | |
|-----------------|--|
| End point title | Change from baseline in MDS UPDRS part 1 On medication at 60 weeks |
|-----------------|--|

End point description:

Movement Disorder Society Unified Parkinson's Disease Rating Scale part 1 non-Motor Experiences of Daily Living subsection score.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 60 weeks post randomisation.

| End point values | Exenatide | Placebo | | |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 9.3 (\pm 4.0) | 10.1 (\pm 5.3) | | |

Statistical analyses

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
|-----------------------------------|----------------------------|

Statistical analysis description:

For secondary outcomes, the differences between the two groups were summarised using estimates and confidence intervals, using the ANCOVA approach. Outcome measures in the ON medication state were additionally adjusted for change from baseline in LED to account for the possible confounding effect of increased Parkinson's medication during the trial.

| | |
|---|---------------------|
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.22 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 0.8 |

Secondary: Change from baseline in MDS UPDRS part 1 On medication at 48 weeks

| | |
|-----------------|--|
| End point title | Change from baseline in MDS UPDRS part 1 On medication at 48 weeks |
|-----------------|--|

End point description:

Movement Disorder Society Unified Parkinson's Disease Rating Scale part 1 non-Motor Experiences of Daily Living subsection score.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
At 48 weeks post randomisation.

| End point values | Exenatide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 29 | | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 8.8 (± 4.4) | 9.7 (± 5.6) | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|---|----------------------------|
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.21 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | 1.5 |

Secondary: Change from baseline in MDS UPDRS part 2 On medication at 60 weeks

| | |
|---------------------------------|---|
| End point title | Change from baseline in MDS UPDRS part 2 On medication at 60 weeks |
| End point description: | Movement Disorder Society Unified Parkinson's Disease Rating Scale part 2 Motor Experiences of Daily Living subsection score. |
| End point type | Secondary |
| End point timeframe: | |
| At 60 weeks post randomisation. | |

| End point values | Exenatide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 11.6 (± 6.6) | 11.0 (± 6.7) | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|---|----------------------------|
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | 1.5 |

Secondary: Change from baseline in MDS UPDRS part 2 On medication at 48 weeks

| | |
|---|--|
| End point title | Change from baseline in MDS UPDRS part 2 On medication at 48 weeks |
| End point description: Movement Disorder Society Unified Parkinson's Disease Rating Scale part 2 Motor Experiences of Daily Living subsection score. | |
| End point type | Secondary |
| End point timeframe: At 48 weeks post randomisation. | |

| End point values | Exenatide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 29 | | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 11.7 (± 6.3) | 10.8 (± 5.6) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | 1.5 |

Secondary: Change from baseline in MDS UPDRS part 3 On medication at 60 weeks

| | |
|---|--|
| End point title | Change from baseline in MDS UPDRS part 3 On medication at 60 weeks |
| End point description: Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 Motor Examination subsection score. | |
| End point type | Secondary |
| End point timeframe: at 60 weeks post randomisation. | |

| | | | | |
|--------------------------------------|-----------------|-----------------|--|--|
| End point values | Exenatide | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | 19.9 (± 10.3) | 14.5 (± 7.1) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.61 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | 0.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 0.9 |

Secondary: Change from baseline in MDS UPDRS part 3 On medication at 48 weeks

| | |
|---|--|
| End point title | Change from baseline in MDS UPDRS part 3 On medication at 48 weeks |
| End point description: Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 Motor Examination subsection score. | |
| End point type | Secondary |
| End point timeframe: At 48 weeks post randomisation. | |

| End point values | Exenatide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 29 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | 20.5 (± 9.5) | 15.7 (± 7.1) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.99 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -0.002 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | 2.4 |

Secondary: Change from baseline in MDS UPDRS part 4 On medication at 60 weeks

| | |
|-----------------|--|
| End point title | Change from baseline in MDS UPDRS part 4 On medication at 60 weeks |
|-----------------|--|

End point description:

Movement Disorder Society Unified Parkinson's Disease Rating Scale part 4 Motor Complications subsection score.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 60 weeks post randomisation.

| End point values | Exenatide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | 5.2 (± 2.3) | 6.1 (± 3.7) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 0.9 |

Secondary: Change from baseline in MDS UPDRS part 4 On medication at 48 weeks

| | |
|-----------------|--|
| End point title | Change from baseline in MDS UPDRS part 4 On medication at 48 weeks |
|-----------------|--|

End point description:

Movement Disorder Society Unified Parkinson's Disease Rating Scale part 4 Motor Complications subsection score.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 48 weeks post randomisation.

| End point values | Exenatide | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 29 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | 4.9 (\pm 2.5) | 5.6 (\pm 3.0) | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|---|----------------------------|
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.48 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 0.9 |

Secondary: Change from baseline in MATTIS Dementia Rating scale at 60 weeks

| | |
|---|--|
| End point title | Change from baseline in MATTIS Dementia Rating scale at 60 weeks |
| End point description: | |
| The Mattis Dementia Rating Scale (DRS-2) assesses a patient's overall level of cognitive functioning with respect to five abilities: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory using a series of 36 tasks and 32 stimulus cards. | |
| End point type | Secondary |
| End point timeframe: | |
| At 60 weeks post randomisation. | |

| End point values | Exenatide | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 28 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | 139.9 (\pm 3.6) | 140.2 (\pm 4.6) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 2.5 |

Secondary: Change from baseline in MATTIS Dementia rating scale at 48 weeks

| | |
|-----------------|--|
| End point title | Change from baseline in MATTIS Dementia rating scale at 48 weeks |
|-----------------|--|

End point description:

The Mattis Dementia Rating Scale (DRS-2) assesses a patient's overall level of cognitive functioning with respect to five abilities: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory using a series of 36 tasks and 32 stimulus cards.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 48 weeks post randomisation.

| End point values | Exenatide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 29 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | 139.7 (± 4.1) | 140.2 (± 3.9) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Exenatide v Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.57 |
| Method | ANCOVA |
| Parameter estimate | Slope |
| Point estimate | 0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1.9 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 60 weeks.

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

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Exenatide |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Exenatide | Placebo | |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 2 / 30 (6.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (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 flutter | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (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 | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Faecal Impaction | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute urinary retention | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Unintentional weight loss | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Exenatide | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 31 / 32 (96.88%) | 29 / 30 (96.67%) | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 3 / 30 (10.00%) | |
| occurrences (all) | 5 | 3 | |
| Nervous system disorders | | | |
| Increased time off medication | | | |
| subjects affected / exposed | 8 / 32 (25.00%) | 11 / 30 (36.67%) | |
| occurrences (all) | 8 | 12 | |
| Sleep disorder | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 6 / 30 (20.00%) | |
| occurrences (all) | 3 | 6 | |
| Increased dystonia | | | |

| | | | |
|---|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | 5 / 30 (16.67%) 5 | |
| Dyskinesia subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 2 | 2 / 30 (6.67%) 2 | |
| Freezing subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 2 / 30 (6.67%) 2 | |
| General disorders and administration site conditions Pain subjects affected / exposed occurrences (all) | 9 / 32 (28.13%) 13 | 6 / 30 (20.00%) 11 | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 12 / 32 (37.50%) 12 | 10 / 30 (33.33%) 11 | |
| Nausea subjects affected / exposed occurrences (all) | 16 / 32 (50.00%) 16 | 8 / 30 (26.67%) 10 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 32 (21.88%) 8 | 4 / 30 (13.33%) 6 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 5 / 32 (15.63%) 5 | 3 / 30 (10.00%) 3 | |
| Loss of appetite subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | 1 / 30 (3.33%) 1 | |
| Indigestion subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 30 (3.33%) 2 | |
| Bloating subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 3 | 0 / 30 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|--|--|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 4 | 3 / 30 (10.00%) 3 | |
| Skin and subcutaneous tissue disorders Injection site reaction subjects affected / exposed occurrences (all) | 25 / 32 (78.13%) 27 | 22 / 30 (73.33%) 26 | |
| Renal and urinary disorders Lower urinary tract symptoms subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 6 / 32 (18.75%) 6 0 / 32 (0.00%) 0 | 6 / 30 (20.00%) 7 2 / 30 (6.67%) 3 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 1 / 30 (3.33%) 1 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 5 / 30 (16.67%) 5 | |
| Metabolism and nutrition disorders Weight loss subjects affected / exposed occurrences (all) Weight gain subjects affected / exposed occurrences (all) | 24 / 32 (75.00%) 24 7 / 32 (21.88%) 7 | 18 / 30 (60.00%) 18 11 / 30 (36.67%) 11 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 09 January 2015 | Protocol updated to v3.0 to add patients with Type 1 or Type 2 Diabetes mellitus to the exclusion criteria. Other corrections and clarifications throughout. |
| 22 May 2015 | Protocol updated to v4.0 with changes in withheld PD medication, participants not being shown an instructional video re lumbar puncture and clarifications throughout. |
| 20 August 2015 | Protocol updated to v5.0 with the additional dispensing of a kit to maintain sufficient IMP supply after a high number of vial breakages. |
| 13 November 2015 | Protocol updated to v6.0 with the following: excessive weight loss resulting in dose temporarily stopped not discontinued and becoming a notifiable event; exploratory outcomes added; additional blood test at visit seven; clarifications. |

Notes:

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.

The small size of our study meant that, despite randomisation with a block design according to Hoehn and Yahr status, the Exenatide group had higher MDS-UPDRS part 3 scores and lower LED at baseline than the placebo group.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28781108>