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

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Background

- Parkinson’s disease (PD) is a progressive neurodegenerative condition.
- Signs and symptoms
  - Motor e.g. tremor, rigidity, slow movement
  - Non-motor e.g. depression, dementia, sleep disturbance
- Management predominantly consists of therapies which aim to relieve the symptoms of PD.
- There is an un-met need for disease modifying therapies which can alter the course of disease progression.
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Background cont.

• Exenatide is a Glucagon-like peptide-1 (GLP-1) receptor agonist, licensed for use in type II diabetes in 2005 for its beneficial effects on glucose homeostasis.

• GLP-1 receptors have been identified throughout the brain and in vitro studies suggested neurotrophic and potentially neuroprotective effects of Exenatide.

Key Question
Can Exenatide be re-purposed as a disease-modifying therapy for Parkinson’s disease?
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Background cont.

• A pilot study on patients with moderate Parkinson’s disease conducted at the National Hospital for Neurology and Neurosurgery showed promising results

• Single-blind trial design

• Treatment- Exenatide injections for 12-months followed by 2-month wash-out

45 patients
Randomly assigned

MDS-UPDRS at 12 Months

EXENATIDE (n=20) mean improvement of 2.7 points

CONTROL (n=24) mean decline of 2.2 points

Primary outcome
MDS-UPDRS (part 3)
Advantage of 4.9 points at 12 months in Exenatide treated patients
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**Trial information**

**Chief Investigator**  Dr Tom Foltynie

**Sponsor**  UCL

**Funding**  Michael J Fox Foundation

**IMP**  Astra Zeneca *(supplied free of charge)*
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Trial Design

- Phase II
- Single centre – National Hospital of Neurology and Neurosurgery
- Double-blind
- 60 patients

- Patients randomised 1:1 to receive either treatment:
  - EXENATIDE
  - PLACEBO

  Once weekly subcutaneous injection
Trial Design cont.

- 60 week trial – 48 weeks of treatment
  12 week washout period

- Detailed evaluations – visit 1- Screening
  visit 2- Randomisation and Baseline
  visit 3- 12 weeks
  visit 4- 24 weeks
  visit 5- 36 weeks
  visit 6- 48 weeks
  visit 7- 60 weeks
Primary outcome

- Comparison of Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS UPDRS) motor sub-score in the practically defined OFF medication state at 60 weeks between patients according to treatment allocation, using ANCOVA to adjust for baseline scores.
Secondary outcomes

- Differences at 48 & 60 weeks for each of the secondary outcomes listed below will be compared between groups according to treatment allocation, (using ANCOVA to adjust for differences at baseline):
  - Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part 3 Motor subsection Off medication score at 48 weeks.
  - MDS-UPDRS part 1,2,3 and 4 On medication scores
  - Mattis Dementia Rating scale (DRS-2)
  - Safety and tolerability of Exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and adverse effects.
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**Trial Timelines**
- Funding received: Jun. 2013
- First participant recruitment: Planned – Dec. 2013
  Actual – 18-Jun-2014
  
  Delay due to acquisition by Astra Zeneca of Bristol Meyers Squibb’s interests in the diabetes alliance.
- Recruitment:

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Patient population

• Men and women with diagnosis of Parkinson’s disease
• Hoehn and Yahr stage ≤ 2.5
• Between 25 and 75 years of age
• On dopaminergic treatment with wearing off phenomena
• Ability to self-administer, or to arrange carer administration of trial drug

Exclusions

• Previous exposure to Exenatide
• Known conditions which would compromise ability to participate
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Sample size

- Primary outcome MDS UPDRS part III Motor subsection at 60 weeks (in the OFF medication state)

- 60 patients divided equally between 2 groups will have 90% power to detect a difference of 5.8 MDS UPDRS points between groups using an ANCOVA analysis to adjust for baseline MDS UPDRS score or 80% power to detect a difference of 5 MDS UPDRS points

- Calculation assumes a common standard deviation of 13, and a correlation of 0.85 between baseline and follow-up
Randomisation

- Randomisation uses online service provider (SealedEnvelope.com)
- 1:1 randomisation using permuted blocks of random length
- Stratified by Hoehn and Yahr score
  
  1.0-2.0 versus 2.5

- Patients replaced if they withdraw before first follow-up assessment at 12 weeks
- 2 patients replaced
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Blinding

• Double-blind trial design
• Identically packaged treatment kits identified by code using Sealed Envelope
• 3 months supply dispensed at each study visit
• Assessing clinician removed from safety/adverse event reporting to ensure blinded assessments
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Assessments

• 3 monthly assessments
• Screening/Baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks and 60 weeks
• Patients assessed for MDS UPDRS in both ON and OFF medication states
• Practically defined OFF medication state
  
  Patients stop prescribed PD medication
  
  8 hours (overnight) Levodopa
  
  ≥ 36 hours in the case of longer acting agents
• Other assessments undertaken ON medication
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Statistical analysis

- Intention-to-treat using information on all patients who complete a minimum of 12 weeks follow-up
- Per-protocol sensitivity analysis

Primary analysis: ANCOVA (analysis of covariance) to compare the effect of treatment arm (Exenatide or placebo) on the difference between MDS UPDRS part 3 scores in the OFF medication state at 60 weeks, adjusting for baseline MDS UPDRS score and Hoehn and Yahr score.

Missing data: In the event of substantial missing data, a mixed model approach will be used incorporating information from earlier time points.
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Oversight

• Independent Data Monitoring Committee (IDMC) have twice reviewed safety and accumulating efficacy data
  30 patients reached 24 weeks follow-up (Jun 2015)
  60 patients reached 24 weeks follow-up (Oct 2015)

• Recommended trial continuation to Trial Steering Committee (TSC)
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**Trial status**

- Last patient assessment took place on 12 May 2016
- Data entry and queries

- Trial results will determine next steps
- Expected Summer 2016
Thank you for listening

• Any questions?