**The effect of a GLP-1 agonist in patients with a dual diagnosis of Parkinson’s Disease and Type 2 Diabetes Mellitus**

**Sponsor: SVH Sydney**

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**Summary**

|  |  |
| --- | --- |
| **Study Title** | Improvement of Parkinson’s Disease symptoms with a GLP-1 agonist in patients with a dual diagnosis of Parkinson’s Disease and Type 2 Diabetes Mellitus |
|  |  |
| **Objectives** | To demonstrate a significant change in primary outcome  measure of change from baseline of OFF Med UPDRS 3 score at  12 months. Secondary outcome measures include UPDRS  improvement at 3, 6 months and change in PDQ 39 quality of  life scores from baseline at 3, 6 and 12 months. Metabolic and  glycaemic control will also be monitored with HbA1c, lipid  profile, weight, waist circumference and BP measurements at  0, 3, 6 and 12 months. |
| **Study design** | Prospective cohort study before and after design |
| **Planned sample size** | N=>12 |
| **Selection criteria** | Dual diagnosis of T2DM and Parkinson’s |
| **Study procedures** | Quantitative & qualitative |
| **Statistical considerations** | Sample size calculation: using a predicted effect size of 0.15  (15% improvement in UPDRS3) and standard deviation of effect  size of 0.15, 12 patients in GLP-1 treated will be required to  detect a significant improvement at p<0.05 level, with power  of 0.9.  Analysis plan: Baseline 3,6, and 12-month OFF Med UPDRS 3  scores will be compared using paired sample t tests to determine significant differences from baseline at 12  months. |
| **Study duration** | 12 months |

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# BACKGROUND

## Disease Background\*

Parkinson’s disease is a progressive neurodegenerative condition due to loss of dopaminergic neurons in the substantia nigra pars compacta [1]. Clinically, patients present with the cardinal features of tremor, bradykinesia, postural instability and rigidity. Other features, such as neuropsychiatric symptoms, cognitive decline and autonomic dysfunction, may also be present. Prognosis is variable however owing to the progressive nature of the disease by 10-15-years many patients experience significant morbidity and loss of independence. Factors including age of onset, genetic profile and clinical phenotype may predict the rate and severity of neuronal loss and functional decline. Dopamine-replacement therapies are symptomatic in alleviating cardinal motor symptoms and some non-motor symptoms and are not thought to favourably modify underlying neurodgenerative progression of the disease. However dopaminergic therapy does favourably alter the clinical disease course improving survival, maintaining functional independence and quality of life [2]. Despite improvements delivered from symptomatic dopaminergic therapies, gradual disease progression continues to occur and remain untreatable with currently available therapies.

## Rationale for Performing the Study

In 2017, a paper was published by the Lancet that showed that exenatide, a GLP-1 receptor agonist, had possible neuroprotective effects in Parkinson’s Disease during a single-centre, randomised trial (n=62) that assigned 2mg Exenatide versus placebo once weekly in addition to their regular PD medications [3]. These patients were non-diabetic and the GLP-1 treatment arm showed a modest improvement in OFF Med UPDRS3 score at 12 months. Our project aims to determine whether the use of a GLP-1 agonist in patients with Parkinson’s AND diabetes improves motor Parkinson’s symptoms. We hypothesise that if impaired glucose handling is shared pathogenetic mechanism in both type 2 diabetes and PD then PD patients with diabetes may stand to benefit more from GLP1-agonsist therapy than non-diabetic PD patients studied so far in the existing literature. A positive outcome from this study has the clinical potential for adjusting the existing diabetes management of this patient population. Both disease processes could be targeted with a medication that is already the standard of care for one.

# STUDY OBJECTIVES\*

Does treatment of diabetes with a GLP-1 agonist improve Parkinson’s motor symptoms and quality of life?

## Primary Objective\*

Demonstrate a significant improvement in motor symptoms of Parkinson’s disease as determined by change from baseline of OFF Med UPDRS 3 score at 12 months.

## Secondary objectives

Secondary outcome measures include UPDRS improvement at 3 and 6 months and change in PDQ 39 quality of life scores from baseline at 3, 6 and 12 months. Glycaemic control from

the use of a different diabetic medication should also be maintained.

# STUDY DESIGN\*

## Design\*

Prospective open-label cohort study with before and after design.

## Study Groups

The study group patients with a dual diagnosis of T2DM and Parkinson’s, treated with a GLP-1 agonist. A small number of PD patients who are recruited and referred for GLP-1 agonist treatment, but be deemed unsuitable or decline treatment, will be invited to participate in the clinical assessments as an untreated subgroup. Control patients will not be receiving Bydureon therapy, or having any of their regular therapy altered, but will undergo the same monitoring interventions as the Bydureon-treated group at baseline, 3 months, 6 months and 12 months.

## number of participants

We anticipate from our sample size calculations that >12 patients with diabetes and PD will be required to complete the study

## number of SITES

St Vincent’s hospital and St Vincent’s Clinic for patient recruitment with clinical assessments undertaken in St Vincent’s Hospital.

## duration

12 months

Start date ~ May-July, as permitting with the current COVID-19 climate

3-month data will be reported on for the purposes of ILP

# PARTICIPANT SECTION

## Inclusion Criteria\*

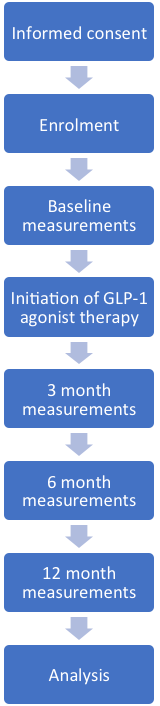
* Diagnosis of Parkinson’s disease meeting UK Brain Bank Criteria
* Diagnosis of Type 2 Diabetes not receiving GLP-1 agonist therapy
* HbA1c ≥ 7 %
* Willingness to give written informed consent and willingness to participate to and comply with the study.
* Patients with cognitive impairment sufficient to impair capacity to provide informed consent are excluded from the study (MMSE<24)
* Age >45 years

## Exclusion Criteria\*

* Patient incapable of providing informed consent
* Patients receiving insulin treatment for type 2 diabetes
* Contraindications to Extended release Exentatide (Bydureon) therapy including: pregnancy, Multiple Endocrine Neoplasia Type 2, Medullary Carcinoma of the thyroid, active Crohn’s disease or Ulcerative colitis, gastritis or severe gastroparesis, pancreatitis and chronic renal impairment with eGFR<30 ml/min

# STUDY OUTLINE\*

## Study Flow Chart



## Investigation plan

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| List Interventions | Enrolment Visit | Visit 1 | Visit 2 | Visit 3 and 4 | Final Study Visit |
| Informed Consent | ✔ | Baseline assessments | Commencement of GLP1-agonist | UPDRS 3 OFF Med  PDQ 39 | UPDRS 3 OFF Med  PDQ 39 |
| Inclusion / Exclusion criteria | ✔ | UPDRS 3 OFF Med  PDQ 39 |  |  |  |
| History |  | ✔ | ✔ | ✔ | ✔ |
| Physical examination |  | ✔ | ✔ | ✔ | ✔ |
| Adverse Event & Serious Adverse Event Assessment |  | ✔ | ✔ | ✔ | ✔ |

Methodology: Patient assessments of motor function will be undertaken in an OFF-med condition defined as morning assessment of patients who have not taken their morning PD medication. Assessment in the medication OFF state reduces the effect of symptomatic dopaminergic medication on motor state, which may fluctuate and overwhelm smaller treatments effects of GLP1-agonist. All study subjects will receive the intervention (GPL1-agonist treatment) in an open label manner. The control group will undergo the same interventions at baseline, 3 months, 6 months and 12 months to determine glycaemic control and severity of Parkinsonian symptoms. Our sample size calculation determines 12 subjects will be required to detect a significant improvement in OFF med UPDRS at 12 months.

Data Collection: Patient demographic information including age, gender, disease duration, usual medications, with be collected from review of cases notes and patient files. The materials required for the study are all contained within St Vincent’s Hospital and St Vincent’s Clinic patient records. Clinical data will be collected in the form of Parkinson’s disease motor symptoms assessed prospectively in the OFF med condition using the UPDRS 3 rating scale, the primary outcome measure of the study. Quality of life will be assessed using the PDQ 39 rating scale, one of the secondary outcome measures. Glycaemic control will be assessed at 0, 3, 6 and 12 months with HbA1c, lipid profile, weight, waist circumference and BP measurements.

## Study Procedure Risks

The study intervention is administration of GLP1-agonist Exenatide extended release (Bydureon) 2mg subcutaneously weekly. The study group will have been selected to have Types 2 diabetes and eligible to receive Bydureon as part of optimisation of their diabetes treatment and standard clinical care. As such the intervention is both TGA and PBS approved and justified irrespective of whether they were to participate in clinical assessments of PD motor function. The risks of Bydureon therapy include nausea, vomiting, diarrhoea weight loss, worsening of chronic renal impairment, hypoglycaemia, pancreatitis, allergic reactions and injection site reactions. The risks of serious adverse events are low, and in general Bydureon is considered safe and well tolerated, and widely used as an existing approved type 2 diabetes therapy. Risks are further mitigated by exclusion of patients unsuitable for Bydureon therapy (see exclusion criteria 4.2).

## Recruitment and Screening

Participants will be recruited from the movement disorders outpatient clinic at St Vincent’s Hospital and St Vincent’s Clinic. Investigators will screen potential participants to determine whether they fulfil the criteria of the study. Screening will involve determining whether or not patients have a dual diagnosis of Type 2 Diabetes Mellitus and Parkinson’s Disease as determined through patient records at the Movement Disorders Clinic at St Vincent’s Public Hospital and the private rooms of Dr Stephen Tisch. A patient list will then be given to Dr Stephen Tisch to determine whether they fit the inclusion criteria. Patients deemed suitable by Dr Stephen Tisch will be passed on to Prof. Jerry Greenfield to determine their suitability in receiving Bydureon as a therapy. Investigators will then approach potential participants to obtain their informed consent. An initial meeting with Prof. Greenfield will also consider who will be responsible for administering the Bydureon injection and whether participants will qualify for PBS-subsidised treatment. The participants’ treating physician will be consulted regarding suitability to participate in the study. Participants will be given a copy of the (information sheet and consent form), and its contents will be explained to the participants. During baseline measurements, a diabetes educator will approach patients deemed eligible for the treatment. The educator will instruct them on how to use the Bydureon injections. If it has been indicated that a carer will be responsible for this injection, they will be asked to attend this consultation so that they may receive the education from the diabetes educator. All participants will be given the opportunity to ask questions.

## Informed Consent Process

The participant will be given a copy of the information sheet and consent form. Participants will be given sufficient time to read and contemplate the information sheet. The study procedure and purpose will be explained to the participant, and any questions answered.

## Enrolment Procedure\*

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study enrolment number, and this will be documented in the participant’s medical record and on all study documents.

## Randomisation Procedure

N/A: non-randomised study.

# Adverse events and early termination

## Adverse Event Reporting

The proposed study protocol carries low risks. The Bydureon therapy is taking place within the context of approved clinical treatment for type 2 diabetes supervised by an experienced Endocrinologist, and is justified for optimisation of type2 diabetes irrespective of potential impacts on concurrent Parkinson’s disease. The study assessments are inherently safe and consist of clinical rating scales and questionnaires performed prospectively by the examiner. In the case of an adverse event, participants are to inform the attending medical officer and investigators immediately.

## Serious Adverse Event Reporting

It is unlikely a serious adverse event will result from the proposed study protocol. A serious adverse event includes any of the following: death, life-threatening consequences, requires inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital/birth defect, condition requiring unnecessary medical or surgical intervention. Any serious adverse events and their impact on the study will be evaluated and reported to HREC in the annual report, as applicable. The NHLBMD safety reporting template will be referred to. Furthermore, if participant suffers any injuries or complications as a result of this study, he/she should contact their doctor and the investigators of the study as soon as possible, and the participant will be assisted in arranging appropriate medical treatment. Participants have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if the injury or complication is caused by the procedures, or by the negligence of any of the parties involved in the study. If participant receive compensation that includes an amount for medical expenses, he/she will be required to pay for his/her medical treatment from those compensation monies. If the patient is not eligible for compensation for their injury or complication under the law, but are eligible for Medicare, then he/she can receive any medical treatment required for their injury or complication free of charge as a public patient in any Australian public hospital. Participants will be advised of this in the information sheet.

## Data Safety and Monitoring Board

Our study intervention drug (Bydureon) is already approved for clinical use for the indication in our patient group (type 2 diabetes). Furthermore, our study is not industry sponsored but instead investigator initiated. As Bydureon is already approved for use in the study group, we do not envisage any safety issues beyond those encountered with this medication as currently used in clinical practice. We do not believe reporting to a data safety and monitoring board will be required. We will be reporting any safety issues as required by the NHLBMD safety reporting template.

## Early Termination

We anticipate that a very small number of subjects will terminate the study early. Reasons for early termination may include patient preference, change in personal circumstances or adverse events. Our study design includes assessment of outcome at 3, 6 and 12 months such that early termination may still allow partial data analysis.

If patients indicate that they do not want their data to be used in the study following withdrawal, their study will not be included in the results or analysis. We will indicate in the methods that ‘x’ number of patients had withdrawn from the trial and that of this ‘x’ number of patients, ‘y’ number of patients chose to withdraw consent for the use of any material collected. Their information will be stored as required for 15 years in the secure location in St Vincent’s Hospital. For patients that do not indicate that they do not want their data to be used in their study, their data collected will be included in the statistical analysis. Again, we will indicate in the methods that of ‘x’ number of patients that had to withdraw, we have included any available data for ‘z’ number of patients. We will adjust the analysis as required and will also include a flowchart in the methods to display this information graphically.

# OUTCOMES AND FUTURE PLANS

The current study is effectively a pilot study with a deliberately simple design to minimise the number of study subjects required to ensure adequate recruitment. If results are of this pilot study are positive and we are able to demonstrate improvement in Parkinson’s motor symptoms following 12 months of Bydureon treatment for type 2 diabetes, we would like to consider a larger more sophisticated study with a prospective randomised, double blind design in the same patient population.

**7.1 STATISTICAL CONSIDERATIONS**

For sample size calculation we have used a conservative predicted effect size of 0.15 (15% improvement in UPDRS 3) and standard deviation of effect size of 0.15. Based on these predicted effect sizes, 12 patients in GLP-1 treated will be required to detect a significant improvement at p<0.05 level, with power of 0.9. Baseline 3, 6, and 12 month OFF Med UPDRS 3 scores will be compared paired sample t tests.

# CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS

Study documents will be collected and stored in a locked cabinet in a secured location in the hospital. The study documents will be stored in the Neurophysiology Clinic on Level 4 Xavier of St Vincent’s Public Hospital, Sydney. The data entered on the electronic spread sheet will be coded and re-identifiable. All data collected will be kept stored securely for 15 years, in accordance with the National Statement on Ethics Conduct, as well as NSW Health data storage requirements under the Health Records and Information Privacy Act, and will be destroyed thereafter. Paper records will be disposed in confidential recycling bins and electronic files will be permanently deleted.

# OTHER STUDY DOCUMENTS

Patient information and Consent form

# RESOURCES

The study does not seek additional resources or materials. The intervention is standard clinical care (Bydureon therapy for type 2 diabetes). The outcome measures are printed PD rating scales and questionnaires with negligible cost. The investigators do not seek remuneration for the study.

# REFERENCES\*

[1] <https://www.uptodate.com/contents/etiology-and-pathogenesis-of-parkinson-disease?sectionName=EPIDEMIOLOGY&search=parkinsons%20disease%20adult&topicRef=4903&anchor=H14&source=see_link#H1>

[2] <https://www.uptodate.com/contents/etiology-and-pathogenesis-of-parkinson-disease?sectionName=EPIDEMIOLOGY&search=parkinsons%20disease%20adult&topicRef=4903&anchor=H14&source=see_link#H14>

[3] Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, Hibbert S, Budnik N, Zampedri L, Dickson J, Li Y, Aviles-Olmos I, Warner TT, Limousin P, Lees AJ, Greig NH, Tebbs S, Foltynie T. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10103):1664-1675<https://www.nhmrc.gov.au/guidelines-publications/e72>?