1.0 Synopsis

Title	A prospective observational study to evaluate the clinical outcomes and burden of disease of PD patients with motor fluctuations not adequately controlled by current PD medications.
Sponsor (Responsible Party)	AbbVie* * The specific details of the AbbVie legal entity within the relevant country are provided within the Non-Interventional Study (NIS) agreement with the Investigator/Institution.
Rationale and Background	Parkinson's Disease (PD) is a neuro-degenerative disease without a cure or disease-modifying therapies available. As the disease progresses, many patients suffer from erratic gastric emptying resulting in reduced absorption of oral medications (such as oral levodopa) as well as synaptic plasticity, leading to motor complications which can be debilitating to both the patients and their caregivers. Due to many reasons including limited access to advanced therapies, the majority of the patients are treated with a polypharmacy approach based often leading to a complex regimen of frequent daily intakes of many different drug classes. These regimens may lead to decreased medication adherence, resulting in poor symptom control, as well as increased adverse effects. Poor symptom control leads to a poor quality of life for the patient, increased caregiver burden and additional cost to the healthcare system (increased healthcare utilization).
Research Question	There is limited data available on the clinical outcomes and disease burden of patients who are experiencing motor fluctuations not adequately controlled by current PD medications. Data from a real-world setting in this patient population will help to understand the disease burden and its evolution over time, and the impact of advanced therapies.
Objectives and Endpoints	The objective of this Observational study is to describe the clinical outcomes and the burden of disease in PD patients with motor fluctuations not adequately controlled by current PD medications. **Primary endpoint** Change in Off time from baseline to 24 months (as measured by PD diary)

	Secondary endpoints • Change in Off time from baseline to 12 months • Change in dyskinesia time from baseline to 12 and 24 months • Change in Hoehn and Yahr (HY) Stage (in ON and OFF state) from baseline to 12 and 24 months • Change in Euro Quality of Life Questionnaire 5 Dimensions and 5-Level (EQ-5D-5L) Total patient and caregiver score from baseline to 12 and 24 months • Change in Unified Parkinson's Disease Rating Scale (MDS UPDRS) part II score from baseline to 12 and 24 months • Change in Non-Motor Symptoms Scale (NMSS) Total score from baseline to 12 and 24 months • Change in Parkinson's Disease Questionnaire-39 (PDQ39) summary index from baseline to 12 and 24 months • Change in Healthcare Resource Utilization (HCRU) over a period of 12 and 24 months • Change in WPAI Total Score over a period of 12 and 24 months • Change in comedications during the 12- and 24-months observational follow-up • Treatment pattern and change in the clinical outcomes listed above after 12 and 24 months in patients on oral medication vs patients with additional rescue medications (Apo injection, Sublingual Apo medication or inhaler Levodopa) and patients remaining on oral medication vs patients who initiated DAT. **Exploratory endpoints** • Modified Caregiver Stress Index (MCSI) Total score over a period of 12 and 24 months • Detailed patient interview on the patients´ reasons for selecting or declining device-aided treatment (DAT, if applicable) • PD symptoms as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device (if available locally and compliant per local regulations) from Baseline • Treatment satisfaction measured by Treatment Satisfaction Questionnaire for Medication 9 item (TSQM9) • Patient Global Impression of Change of Severity (PGIC-S) • Change in Parkinson's Disease Sleep Scale-2 (PDSS-2) Total score from baseline to 12 and 24 months • Change in Mini-Mental State Examination (MMSE) Total Score from baseline to 12 and 24 months

	Safety Measures Any Adverse Event reporting will follow local rules and regulations. In the US, any AEs observed must be reported to the FDA or the manufacturing company of the suspect product.
Study Design	**Overall Study Design:** Prospective, multi-country, observational, study evaluating the disease progression of advanced PD patients experiencing motor fluctuations not adequately controlled by current PD medications.
Study Size	**Number of study sites:** Approximately 90 sites globally.
Subject Population	**Number of Subjects to be Enrolled:** Approximately 550 adult subjects with PD whose motor symptoms are inadequately controlled by oral medications **Inclusion Criteria for study population** 1) Subjects with diagnosis of idiopathic PD that is levodopa –responsive 2) Subjects must be judged by the investigator to have had an adequate trial of available oral medications and be inadequately controlled by current therapy, with a minimum of 2.5 hours of "Off" time per day 3) Must have a recognizable/identifiable "Off" and "On" state (motor fluctuations) as established through investigator observation and confirmed by self-report recorded at the baseline visit. 4) Subject must be an adult male or female, 30 years of age, or older. 5) Subject must be able to understand the nature of the study and have had the opportunity to have any questions answered by the investigator. 6) Subject is willing and able to comply with procedures required in this protocol. 7) Subject, if judged by the investigator to have decision making capacity, must voluntarily sign and date an informed consent form approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to initiation of any study-specific procedures. In the absence of subject's ability to provide informed consent, the informed consent form must have been signed by a person who has the legal right to act on behalf of the subject following national laws. 8) Subject does not have a clinical diagnosis of dementia and has MMSE score of 24 or greater. Subjects with mild cognitive impairment (MMSE score of 19 – 23 inclusive) may be enrolled if in the investigator's opinion, are able to adhere to all study requirements.

	Subjects with moderate or severe impairment (MMSE scores of 18 or below) may not be enrolled. **Exclusion Criteria for study population:** 1) Atypical parkinsonism 2) A recent (within 6 months prior to study inclusion) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator 3) A history or presence of psychotic episodes that in the investigator's judgment are not adequately controlled. 4) Clinically significant unstable medical conditions or any other reason that the investigator determines would interfere with the subject's participation in this study. 5) Subjects treated with DAT at enrollment. 6) Participation in a concurrent interventional clinical trial .
Sample size and Justification	The standard deviation for OFF time changes from baseline is estimated to be around 3 hours based on some previous studies [1,2] in Parkinson's Disease. The estimated precision, given by half width of the 95% confidence interval, and the 95% confidence intervals under different sample sizes, mean OFF time change and assumed standard deviation were provided in the table 1 below. The R version 3.5.1 was used for the calculation. Assuming the standard deviation to be 3 hours, the sample sizes of 50 to 550 give us the estimation precision between 0.83 to 0.25 for the mean change of OFF time from baseline. The sample size of the study is 550. With a sample size of 550 patients, the estimation precision is 0.25 hours for mean change of OFF time from baseline.
Statistical methods	There is no pre-specified hypothesis testing for this descriptive study. Descriptive statistics will be used to summarize all endpoints. Continuous endpoints will be summarized using number of missing and non-missing observations, mean, median, minimum, maximum, standard deviation and 95% confidence interval. Categorical variables will be summarized as the number of patients and percentages (%) of patients in each category. The count of missing observations will be provided in all tables. All collected data will be listed. Two interim analyses will be performed after 50% of patients and after 100% of enrolled patients have been followed for 12 months.