4. Study Synopsis

Title:	EpiPark – Advanced Parkinson's disease treatment eligibility in France: an epidemiological study.
Rationale and Background:	Parkinson's disease (PD) is a progressive neurodegenerative condition which is the second most frequent neurodegenerative disorder worldwide, affecting 6.5 million people. In France, the number of patients being registered in the 2013 health care system database as being affected by PD was assessed at 195,200. Considering the aging population, PD represents a real public health problem. As PD is a chronic and slowly progressive disease, symptoms continuously worsen over the years and the combination therapy of conventional, orally-administered Parkinson drugs is no longer sufficient for an adequate symptomatic control. At this stage of the disease, named as advanced, three invasive therapeutic alternatives can be considered: deep brain stimulation (DBS), subcutaneous apomorphine continuous infusion (APO), or continuous intestinal infusion of levodopa-carbidopa gel (Duodopa®). More specifically, Duodopa® is indicated for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. In the context of negotiations with the Economics Committee for Health Products in 2013, AbbVie was asked by the Transparency Committee of the French Authority for Health to reevaluate the French target population of Duodopa® on the basis of new available epidemiological data. Considering that these data were partially inaccurate, the Transparency Committee concluded to a restrictive target population size estimated at 360 patients. In this context, this new epidemiological study aims to accurately estimate in a real-life setting the size of the French population of PD patients who would be eligible for treatment with Duodopa®, according to the conditions defined by the French Authority for Health in its latest Transparency Committee's opinion. As a secondary objective, this population size will also be estimated according to the marketing authorization indication. This study will allow describing characteristics of advanced PD patients. Furthermore, the population size of PD patients eligible for each of the three invasive therapies (DBS, APO and Duodopa®) will be calculated and the ineligibility criteria for these therapies will be described.
Objectives:	The **primary objective** of this study is to estimate, in Metropolitan France, the size of the population of PD patients eligible to Duodopa® in accordance with the conditions defined by the French Authority for Health in its Transparency Committee's opinion. *These conditions are defined as follows:* ▪ *Patients with advanced levodopa-responsive Parkinson's disease presenting severe motor fluctuations and hyper-/dyskinesia* ▪ With *no satisfactory results under combination of antiparkinsonian drugs* ▪ *Not eligible for Deep Brain Stimulation and presenting contra-indication, intolerance or failure to subcutaneous apomorphine continuous infusion*.

	The **secondary objectives** of this study are as follows: ▪ To estimate, in Metropolitan France, the size of the population of PD patients eligible for Duodopa® according to the indication defined by its marketing authorization. *This indication is defined as follows:* - *Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia* - *When available combinations of antiparkinsonian drugs have not given satisfactory results.* ▪ To describe advanced PD patients and disease characteristics (including background history). ▪ To estimate the proportion of PD patients eligible for each invasive therapy (DBS, APO or Duodopa®). An **exploratory objective** will be applied to the study population: to estimate the size of the population of PD patients eligible for Duodopa® when advanced PD criteria are defined by Delphi method.
Study Design:	This is an epidemiological, cross-sectional, descriptive, non-interventional, and multicenter study designed to estimate, in Metropolitan France, the size of the population of PD patients eligible for Duodopa®, in accordance with the conditions defined by the French Authority for Health in its Transparency Committee's opinion. Two complementary parts will be done simultaneously: a CENSUS and a descriptive CORE part.
Population:	PD patients at advanced stage of disease (or their legal representatives), who have received verbal and written information about the study and who did not express their opposition to personal data collection and processing. Participating centers are neurologists (hospital-based, private practice or mixed practice). All study centers are located in mainland France.
Variables:	For the **CENSUS**, the following variables should be documented on weekly forms of the eCRF: ▪ First and last days of work in the week ▪ Number of advanced PD patients seen as outpatients ▪ Number of advanced PD patients seen by another neurologist for PD ▪ Number of yearly medical visits done by the participating neurologist per advanced PD patient ▪ Included patients in the Core descriptive part of the study ▪ Reasons for non-inclusion of eligible patients For the **CORE study**, the following variables should be documented on the eCRF: ▪ Validation of selection criteria ▪ Sociodemographic data ▪ Disease history (including number of visits for PD within the last 12 months, follow-up by another neurologist for PD or not, Levodopa-responsiveness) ▪ Prior and ongoing PD treatments and concomitant therapies ▪ Clinical data ▪ Comorbidities ▪ Advanced PD criteria according to Delphi method (exploratory objective)

Data Sources:	Routine visit data when available as documented in patients' records will be entered in the eCRF.
Study Size:	The sample study will include neurologists from IMS Health OneKey reference files. The sample size calculation is based on the study objective, i.e. to evaluate in Metropolitan France, the size of the population of PD patients eligible for Duodopa® in accordance with the conditions defined by the French Authority for Health in its Transparency Committee's opinion. Since the expected proportion of advanced PD patients which might be eligible to Duodopa®, is not known and there is no evidence supporting it, the worst case hypothesis will assume a proportion of 50%. For a confidence interval of 95% and a precision of 5%, a total of 384 assessable patients will be needed in the CORE descriptive part of the study. In order to take into account non-assessable patients (estimated at 15%), a sample of 442 advanced PD patients in this study part will be recruited by approximately 289 neurologists (approximately 339 neurologists will be selected to consider the inactive neurologists, estimated at 15% of all the participating physicians). To ensure the representativeness of the sample of recruited neurologists, a two-level stratified design will be considered. The two criteria used will be: the type of medical practice (hospital, private center, mixed activities) and the geographic location (5 regions corresponding to the French 'phone areas').
Statistical Analysis:	The statistical analysis will be conducted using the SAS® software (SAS Institute, North Carolina, USA) V9.2 (or higher) on Windows™. Results will be presented, overall, and per type of practice of the neurologist visited. Continuous variables will be described by the number of valid cases and missing data, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Categorical variables will be described as the total number and relative percentage per category. No missing data will be replaced. Confidence intervals of 95% will be calculated when relevant. Calculations will first be performed on raw data, and then adjusted and weighted to accurately reflect the population of neurologists and advanced PD patients the study seeks to measure. Statistical adjustments will be implemented to correct for potential duplicates (both CENSUS and CORE part of the study), incompleteness of CENSUS weekly reports, and non-inclusion of eligible patients in the CORE part. Statistical extrapolations will ensure generalizability of the results over 1 year of activity and the actual proportion of recruited neurologists in each stratum (if required).
Milestones:	Start of data collection: Q2 2017 End of Data collection: Q1 2018 Final Study report: Q3 2018