1. Title Page

AbbVie

Medical Research /Research Plan No. 11 262

EPI PARK
Advanced Parkinson's disease treatment eligibility in France: an epidemiological study.

Product Name:	None
Type of Study:	Observational Medical Research
Date:	6 FEB 2017
Biometrics:	ICTA PM 11, rue du Bocage 21121 FONTAINE LES DIJON
Sponsor(s):	AbbVie 10, rue d'Arcueil 94528 RUNGIS Cedex FRANCE

This study will be conducted in compliance with this research plan and all applicable regulatory requirements

2. Table of Contents

3. Glossary of Abbreviations

ADELF	Association of French-speaking Epidemiologists (*Association des Epidémiologistes de Langue Française*)
ANSM	French Competent Authority *(Agence Nationale de Sécurité du Médicament)*
APO	Apomorphine
CEPS	Economics Committee for Health Products (*Comité Economique des Produits de Santé*)
CI	Confidence Interval
CNEDiMTS	Transparency Committee for medical devices (*Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé*)
CNOM	French National Medical Council (*Conseil National de l'Ordre des Médecins*)
COMT	Catechol-O-Methyl Transferase
CRA	Clinical Research Associate
CRO	Contract Research Organization
DBS	Deep Brain Stimulation
DCCI	DiCyclohexyl Carbodiimide Inhibitor
DOM	Oversea Department *(Département d'Outre Mer)*
eCRF	Electronic Case Report Form
HAS	French Health Authority (*Haute Autorité de Santé*)
MAO-B	MonoAmine Oxidase-B
MRI	Magnetic Resonance Imaging
NA	Not Applicable
PD	Parkinson's disease
PMSI	Medicalized Information System Program (*Programme de Médicalisation des Systèmes d'Information)*
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
UPDRS	Unified Parkinson Disease Rating Scale
Std	Standard deviation
TOM	Oversea Territory *(Territoire d'Outre Mer)*

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

5. Introduction

5.1 Epidemiology of Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative condition resulting from a selective degeneration of dopamine-producing neurons in the substantia nigra in the brain stem and the consequent dopamine shortage in the striatum. Genetic causes and non-genetic risk factors play important roles in PD but the exact mechanisms underlying these processes are still not completely understood.

PD is the second most frequent neurodegenerative disorder worldwide, affecting 6.5 million people. There is an increase of prevalence with age and a higher prevalence and incidence of PD in males. In France, this disease affects about 1% of the population aged 65 and over. According to a public study based on data from 2000, the prevalence of treated PD was approximately 143,000 patients in all of the health care systems (Bertin et al, 2005) but it was probably underestimated. More recently, the number of patients being registered in the 2013 health care system database as being affected by PD was assessed at 195,200 (191,500 for Metropolitan France, SG/DGOS 2015). Considering the aging population, PD represents a real public health problem.

5.2 Diagnosis, PD Stages and Drug Therapies

5.2.1 PD Diagnosis, Early Symptoms and Treatments

According to currently applied diagnostic criteria, the clinical syndrome of parkinsonism is characterized by resting tremor, bradykinesia, rigidity, and postural imbalance and it is diagnosed when at least two of these so-called cardinal signs are present (Litvan et al, 2003). Furthermore, PD diagnosis requires that parkinsonism is idiopathic, i.e. that potential causes of secondary parkinsonism (dementia, use of antipsychotic medications, vascular disease, head trauma, infections and other neurodegenerative diseases that involve the nigrostriatal system) are excluded. A good response of symptoms to levodopa medication is often considered supportive for PD diagnosis, although it is not observed in all PD patients (Gelb et al, 1999).

Although PD is predominantly a movement disorder, other impairments frequently develop including psychiatric problems such as apathy and depression, neuro-vegetative problems such as orthostatic hypotension and hypersalivation, as well as sleep disorders or pain.

While therapies for PD are as yet only symptomatic, they aim at improving the symptoms of the disease by increasing or substitute for dopamine. Levodopa, the immediate precursor of dopamine, is the "gold standard" symptomatic treatment for PD. It is the most commonly prescribed and effective drug for controlling PD symptoms, particularly bradykinesia and rigidity. Drugs from other therapeutic classes are also used to compensate the lack of dopamine, such as dopamine agonists or inhibitors that block the metabolism of dopamine and its precursors (COMT inhibitors, MAO-B inhibitors).

5.2.2 Advanced PD and Invasive Therapies

As PD is a chronic and slowly progressive disease, symptoms continue to worsen over a period of years but there is no clear consensus on how to define the stages of Parkinson's disease and no diagnostic codes available to classify advanced PD. It is the reason why a recent study aimed to achieve consensus among movement disorder specialists treating PD patients, notably to identify the clinically important indicators that define advanced PD, using the Delphi method (Antonini et al, 2015). However, advanced PD is usually characterized by motor complications inclusive of fluctuations and dyskinesia (Hauser et al, 2006) which dramatically impair patients' quality of life. Usually defined by these motor complications (Hoehn and Yahr Scale stage 4 or 5; Hoehn et al, 1967), late stage symptoms could also include cognitive and psychotic problems (Varanese et al, 2010) evaluated by the Unified Parkinson Disease Rating Scale (UPDRS, Ramaker et al, 2002).

In such cases, the combination therapy of conventional, orally-administered Parkinson drugs is no longer sufficient for adequate symptomatic control for the patient.

At this stage of the disease, three invasive therapeutic alternatives can be considered (Giugni et al, 2014): deep brain stimulation (DBS), subcutaneous apomorphine continuous infusion (APO), or continuous intestinal infusion of levodopa-carbidopa gel (Duodopa®):

- DBS is a functional neurosurgical technique that can be used to treat motor fluctuations, dyskinesia, and tremor and its efficacy was supported by clinical trials (Deuschl et al, 2006; Weaver et al, 2009; Williams et al, 2010). However, symptoms unresponsive to levodopa such as cognitive impairment, gait instability, mood disorders, speech impairment and autonomic dysfunction are unlikely to improve with DBS, and could even worsen (Rocchi et al, 2012).
- APO showed to be effective in treating motor symptoms (Garcia et al, 2008) and some non-motor advanced PD symptoms (Martinez-Martin et al, 2011).
- Duodopa® can be delivered directly to the duodenum or jejunum via a percutaneous endoscopic gastrojejunostomy tube connected to a portable infusion pump. This pump therapy can be used to avoid erratic gastric emptying and to improve intestinal absorption of levodopa (Antonini et al, 2009). This levodopa intestinal gel is an effective treatment for improving motor fluctuations and quality of life scores when compared to conventional therapy as shown by several studies (Nyholm, 2012; Foltynie et al, 2013; Fernandez et al, 2013; Olanow et al, 2014).

6. Rationale

Duodopa® is approved in Europe from January 21, 2004 (international birth date; Sweden) and from September 14, 2004 in France in the following indication: 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 (Duodopa® SmPC). In France, the Transparency Committee limited Duodopa® to the patients not eligible for DBS and presenting contra-indication, intolerance or failure to APO (Duodopa® Transparency Committee opinion, 2006). The estimation of the French target population was then very limited: around 1,000 patients.

In the context of negotiations with the Economics Committee for Health Products (*Comité Economique des Produits de Santé*, CEPS) 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 [data from the '*Programme de Médicalisation des Systèmes d'Information'* (PMSI) between 2006 and 2010; DUOCIBLE, results from an observational study conducted in a single French region]. Considering that these data were partially inaccurate (questioning about the definition of advanced PD for data extracted from the PMSI; questioning about the definition of patients eligible for Duodopa® therapy and number of participating centers in DUOCIBLE), the Transparency Committee concluded to a more restrictive target population size estimated at 360 patients. Only patients non-eligible for DBS and with contra-indication, intolerance or failure to APO should receive treatment with Duodopa® (Duodopa® Transparency Committee opinion, 2013).

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 Duodopa® therapy, 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 also allow describing characteristics of advanced PD patients and estimating the proportion of PD patients eligible for each invasive therapy (DBS, APO or Duodopa®).

7. Study Objectives

This is an observational study. Therefore it is not designed to identify or quantify a safety hazard relating to an authorized medicinal product.

7.1 Primary Objective

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.

N.B.: Contra-indications and precautions for Duodopa® use should be taken into account for the eligibility assessment as they are defined in the drug SmPC (ANSM, Duodopa®).

7.2 Secondary Objectives

The secondary objectives 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®).

Eligibility criteria for DBS and APO are defined as follows:

  - The selection criteria and contra-indications for DBS are specified in the CNEDiMTS opinion (*Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé*) published for all medical devices available in France (CNEDiMTS for medical devices is equivalent to Transparency Committee for drugs). The last published one will be used as reference (HAS, CNEDiMTS opinion, Vercise®, 2015)
  - The indication, contra-indications and precautions for use of APO are defined in the apomorphine SmPC (ANSM, Apokinon®).

7.3 Exploratory Objective

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. The criteria are the following *(Antonini et al, 2015)*:

- Motor symptom indicators:

1. Moderate level of troublesome motor fluctuations
2. At least 2 hours of the day with off-symptoms
3. At least 1 hour of the day with troublesome dyskinesia
4. Moderate level of dyskinesia
5. Troublesome dysphagia
6. Daily oral levodopa doses “5 times a day”

- Non-motor symptom indicators:

1. Mild level of dementia
2. Non-transitory troublesome hallucinations
3. Moderate level of psychosis
4. Non-motor symptom fluctuations
5. Moderate level of nighttime sleep disturbances

- Function indicators:

1. Repeated falls despite optimal treatment
2. Needing help with activities of daily living at least some of the time
3. Not being able to perform complex tasks – most of the time
4. Moderate impaired mobility

8. Observational Plan

8.1 Study Scope

- **A study conducted with neurologists**

In France, PD patients regularly visit neurologists practicing in hospitals (including regional movement disorder expert centers) or working exclusively in private practice or with mixed activities (part time hospital and private practice), even if general practitioners may ensure patients' follow-up and treatment renewal on a regular basis. According to recommendations published by the French Authority for Health (HAS 2014), the PD diagnosis should be confirmed by a neurologist and every 6-month assessment should be performed by a neurologist. This is the reason why the study will be conducted with neurologists only.

- **A study conducted in Metropolitan France**

In order to have a representative sample of French neurologists, it is required to respect the distribution of the different types of practice modalities and the geographical distribution of this specialty (see section 8.5 for more information about physicians' recruitment). The number of neurologists located in overseas territories is very limited (n=35) and distributed over a very large area (5 DOM and 5 TOM). Therefore, a sample able to provide robust information and covering all of these areas seems hardly obtainable. This is the reason why neurologists practicing in the French overseas territories will not be sought in this study.

8.2 Specificities to be considered for this Study

In order to achieve the primary objective of the study, several aspects should be considered:

- The number of visits of PD patients to a neurologist may vary according to patients and centers and range from once every six months up to monthly visits in some occasions (unbalanced treatment, for example).
- The number of practicing neurologists in Metropolitan France is limited compared to other specialties and estimated at 2,611 in 2015 on the basis of the national updated database provided by the independent IMS Health Company (OneKey reference lists).
- The number of patients fulfilling the eligibility criteria to Duodopa® as defined by the French Health Authority appears to be limited.
- A thorough coverage of the target population and the representativeness of the observed samples (neurologists and patients) are key factors in ensuring the quality and the validity of the estimates.

8.3 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.

The design of this epidemiological study will consist of two complementary parts which will be introduced simultaneously:

- A **« CENSUS »** part to count all the idiopathic patients with advanced PD seen consecutively as outpatients by neurologists.

In this part of the study, each participating neurologist will count all the patients seen consecutively in outpatient consultation with a confirmed diagnosis of idiopathic advanced PD. The Census period will be set at 6 months and forms will be completed on a weekly basis. Given the frequency of medical visits of advanced PD patients and the number of participating neurologists in this study (see section 12.5 for the calculation of the sample size), a 6-month period appears to be sufficient for this Census. Furthermore, the 2014 French guidelines recommend that every 6-month assessments of PD patients should be performed by a neurologist (HAS 2014).

- A **« CORE »** descriptive part to describe the characteristics of advanced PD patients and identify patients eligible for Duodopa® and for each of the two other invasive therapeutic alternatives (DBS and APO).

In this part of the study, each neurologist will have to complete Case Report Forms for eligible advanced PD patients previously identified in the Census (see section 8.5.2 for detailed selection criteria of patients). Reasons for non-inclusion of eligible patients will be documented.
The inclusion period is set at 6 months concomitantly to the Census. Given the frequency of medical visits of advanced PD patients, a 6-month period should ensure a complete coverage of the targeted patient profiles and a sufficient potential of patients for the calculation of population sizes. However, a maximum of 10 advanced PD patients included per neurologist will be fixed to avoid a potential 'center effect' in the CORE descriptive part of the study (see section 12.5 for the calculation of the sample size).
In this CORE descriptive part of the study, monitoring procedures, treatments, and concomitant therapies will be decided at the sole discretion of prescribers. The study will only require the collection of data available in patients' records.

8.4 Scientific Committee

An expert Scientific Committee is specifically set up to advice AbbVie, to design this study and to refine and validate the entire project with regard to study design, scientific relevance and objectives, data collection documents, data quality control during the study, and clinical interpretation of statistical results (see Appendix 1).

8.5 Study Conduct

8.5.1 Physician Recruitment, Study Implementation, and Data Collection

- **Neurologists' recruitment**

The statistical unit considered is the neurologist who manages advanced PD outpatients. In 2015, 2,611 practicing neurologists were identified in Metropolitan France and distributed as follows (from the national IMS Health OneKey reference list):

- 1,809 neurologists practicing exclusively in hospitals, representing approximately 69.3% of practicing specialists,
- 425 neurologists working exclusively in private practice (16.3%),
- 377 neurologists with mixed practice (14.4%).

Physicians with private or mixed practice represent about 30% of neurologists.
For hospital-based neurologists, the existence of 25 Movement Disorder Expert centers since 2012 should be noted. Located in hospitals (24 University hospitals and 1 general hospital) and spread all over the French territory (excluding overseas territories), they include neurologists specialized in movement disorders and collaborating with other health professionals in a multidisciplinary approach (nurses, GPs, other specialty physicians, physiotherapists, speech therapists, psychologists, etc.).

At the time of study implementation, the most recent update of OneKey reference list will be used to reflect any changes (e.g. change of address). Retired and inactive neurologists will be deleted, whenever evidence will be available to identify them, as well as neurologists who do not treat patients or who may have a conflict of interest (e.g. physicians employed by regulatory bodies) or with an unknown type of activity (rare) or with a non-applicable sub-specialty (genetics, intensive care, medical imaging, immunology, nuclear medicine, forensic medicine, paediatrics, virology, etc.). The geographical scope will be limited to Metropolitan France.

In order to ensure the representativeness of the sample of recruited neurologists, a two-level stratified selection approach will be considered as these criteria appear to be relevant for our study:

- Type of medical practice (hospital, private, mixed practice) as advanced PD patients with severe symptoms are more likely to be followed-up by hospital-based specialists
- Geographic location (5 regions corresponding to the French 'phone areas') to take into account the distribution of PD patients throughout Metropolitan France, knowing that there is a rising prevalence of PD according to an age North/South gradient.

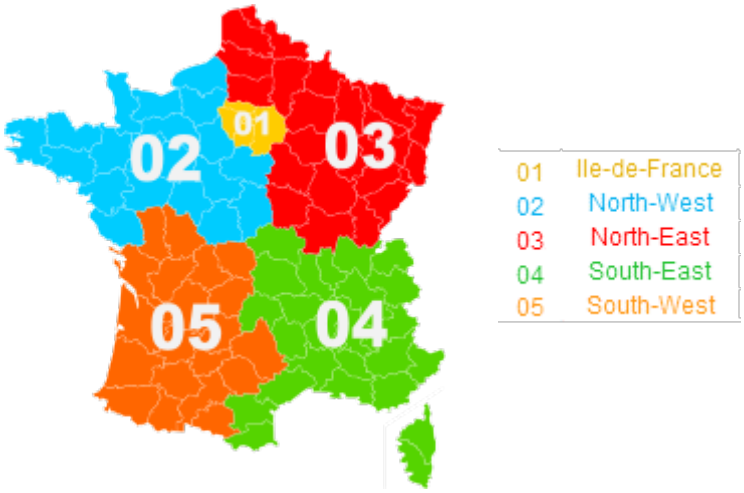

Figure 1: French 'phone areas'

Thus, 15 mutually exclusive strata (a physician can only belong to one stratum) will be defined (3 types of medical practice x 5 geographic locations) with a predetermined number of eligible neurologists to be recruited in each stratum. Other criteria such as age or gender of neurologists appear to be less relevant than type of medical practice and geographic location.

Table 1: Strata definition

Stratum ID	Type of medical practice	Phone area
1	Hospital based	01 Ile-de-France
2	Hospital based	02 North- West
3	Hospital based	03 North-East
4	Hospital based	04 South-East
5	Hospital based	05 South-West
6	Private practice	01 Ile-de-France
7	Private practice	02 North- West
8	Private practice	03 North-East
9	Private practice	04 South-East
10	Private practice	05 South-West
11	Mixed practice	01 Ile-de-France
12	Mixed practice	02 North- West
13	Mixed practice	03 North-East
14	Mixed practice	04 South-East
15	Mixed practice	05 South-West

Each physician from an exhaustive list of practicing neurologists in Metropolitan France (IMS Health OneKey reference lists) – including those practicing in Movement Disorder Expert centers - will be assigned to one of these 15 different strata. Then a draw will be made in each stratum to assign a number to each neurologist. On this basis, phone recruitment of neurologists will be performed in a random order, to reach the predefined enrollment goal in each stratum.

In the following table, the number of neurologists practicing in Metropolitan France and of those who may agree to participate in the study is detailed assuming that 13% (between 10 and 15% from past experience) of French neurologists will be interested to participate.

Table 2: Recruitment plan of neurologists

	Type of medical practice							
	Hospital based		Private practice		Mixed activities		Overall	
Phone area	Total *	May agree to participate	Total	May agree to participate	Total	May agree to participate	Total	May agree to participate
01 Ile-de-France	483	63	72	9	101	13	656	85
02 North- West	276	36	59	8	65	8	400	52
03 North-East	396	51	77	10	66	9	539	70
04 South-East	423	55	136	18	93	12	652	85
05 South-West	231	30	81	10	52	7	364	47
Overall	1,809	235	425	55	377	49	2,611	339

** Including 2 Movement Disorder Expert centers located in the region '01 Ile-de-France', 6 in the region '02 North-West', 7 in the region '03 North-East', 7 in the region '04 South-East' and 3 in the region '05 South-West'*

Reasons for non-participation will be collected during the phone selection of neurologists. In particular, specialists who are not currently treating advanced PD outpatients will be counted in each stratum (see section 0 for more information regarding biases control).
The study is designed to be conducted with a representative sample (according to type of medical practice and geographic location) of around 339 neurologists.
Moreover, assuming that 85% of neurologists will be active in study data collection among those who have agreed to participate in the study, 289 active physicians are expected: 200 hospital-based (69.2%), 47 private practice (16.3%) and 42 mixed activities (14.5%).

- **Study implementation**

After validation of the compliance of financial contract by the monitoring CRO, all the study materials will be transmitted to physicians who agree to participate: study protocol, Patient Informed Consent Forms and eCRF user guide. Physicians will undergo mandatory training over the phone conducted by a Clinical Research Associates (CRA) of the monitoring CRO. The study protocol (detailed objectives and data to be collected) will be explained as well as the procedures for informing patients of the study, the data collection process (data entry in the eCRF and queries for corrections). The names and details of various contacts in AbbVie and in the monitoring CRO will also be disclosed.
At study implementation, neurologists must complete a questionnaire about their involvement in PD patients' management (notably, the number of advanced PD patients seen as outpatients in 2016).
The physician may start the completion of the Census and patients' inclusions in the cross-sectional part of the study only after receiving the training.

- **Data collection**

Over the 6-month study period, each participating neurologist will be asked to:

- Complete the CENSUS part of the study (weekly reports of the number of their advanced PD outpatients seen during the week, even if the neurologist did not see any advanced PD patients over this period). Phone calls and/or e-mail reminders will be regularly performed in the case of non-returned weekly reports. In the case of non-inclusion of eligible patients in the CORE descriptive part of the study, reason for non-inclusion will be collected.
- Include in the CORE descriptive part of the study (detailed information on advanced PD patients registered in the CENSUS) all their consecutive eligible patients having consented to participate in the study (see section 8.5.2 for patient selection criteria). Phone calls and/or e-mail reminders will be regularly performed if the number of inclusions completed is not consistent with the number of included patients as specified in the weekly CENSUS reports. A maximum of 10 advanced PD patients included per neurologist will be fixed to avoid a potential 'center effect'.

All data as detailed in section 8.7 will be collected in an eCRF to be completed by the neurologist on the basis of patients' records.

8.5.2 Patient Selection Criteria

After obtaining regulatory approvals and from the study implementation, eligible patients will be registered in the CENSUS and included in the CORE descriptive part of the study by the neurologists. In the case of non-inclusion of eligible patients, reason for patient's non-participation will be provided on the eCRF (patient's refusal, omission by the specialist, other reason).

The physician will explain the purpose of the study to the patients (or their legal representatives), inform orally and provide the Patient Information Form. He/she will also inform the patients (or their legal representatives) of his/her right to refuse to participate in the study.

Patients' selection criteria are as follows:

- **In the CENSUS part of the study:**
  - Adult (≥18 years old) patient presenting advanced idiopathic Parkinson's disease, defined by a duration of levodopa treatment of at least 3 years and the presence of motor complications (motor fluctuations and/or dyskinesia), insufficiently controlled by conventional anti-parkinsonian medications*
  - Seen by the neurologist as outpatient either in a hospital or a private practice

- **In the CORE descriptive part of the study:**
  - Patient registered in the CENSUS
  - Patient (or legal representative of the patient) who has received verbal and written information about the study and who did not express his/her opposition to personal data collection and processing.

** As there is no consensus definition of advanced Parkinson's disease in France, this definition was retained by the study Scientific Committee as it appears to be wide enough to cover all the patients who could benefit from one of the three invasive therapies (DBS, APO or Duodopa®).*

8.5.3 Site Selection Criteria

On the basis of a national database provided by a company independent from the Sponsor (IMS Health OneKey reference lists), neurologists will be randomly contacted in each stratum (see Section 8.5.1 for the recruitment process). Participation will be only proposed to specialists who manage advanced PD outpatients. This point will be checked during the phone recruitment of neurologists. The number of specialists with no advanced PD outpatients will be counted in each stratum.

8.5.4 Number of Patients

Participating neurologists will be asked to include in the CORE descriptive part of the study all their advanced PD patients registered in the CENSUS until they achieve the maximum quota of 10 patients before the end of the 6-month study period. At least 442 patients are expected to be included in the CORE descriptive part of the study (see section 12.5 for sample size calculation).

8.6 Study Duration

Study duration will be approximately 6 months (between Q2 2017 and Q1 2018) from study implementation to the collected data of the last patient included in the CORE descriptive part of the study.

From study implementation to final study report, the study will last around 17 months (from April 2017 to September 2018).

8.7 Description of Activities

At study implementation, physicians will provide the precise number of advanced PD patients they saw as outpatients in 2016, as well as the confirmation of their involvement in the management of advanced PD patients at the time of the study.

Data to be collected on a specific eCRF for this cross-sectional study are detailed below.

8.7.1 Data collected in the CENSUS

- First and last day of work in the considered week
- Number of advanced PD patients* seen as outpatients
- Number of advanced PD patients* also seen by another neurologist for PD
- Number of yearly medical visits done by the participating neurologist per advanced PD patient* (number of patients with 1, 2, 3, 4 or more visits per year)
- Included patients in the Core descriptive part of the study
- Reasons for non-inclusion of eligible patients (patient having refused to participate, omission by the specialist to propose the study to patients, maximum number of patients inclusions reached, for another reason)

** Duration of levodopa treatment of at least 3 years, presence of motor complications (motor fluctuations and/or dyskinesia), and lack of control under conventional treatments*

8.7.2 Data collected in the CORE descriptive part of the study

Only data available in the patient record will be collected; no additional diagnostic or monitoring procedures will be applied to the patients outside of routine clinical practice.

- Sociodemographic data (age, gender).
- Disease history
    - Follow-up by another neurologist for PD or not
    - Number of visits within the last 12 months
    - Date (year and month) of initial PD diagnosis
    - Date (year and month) of onset of motor complications
- Treatments
    - Antiparkinsonian prior and ongoing treatments
        - Levodopa treatment [start date (month and year), number and dosage of daily oral intakes, reason for discontinuation if applicable (inadequate response, adverse effects, other reason)]
        - Dopamine agonists, amantadine, levodopa + DCCI + COMT inhibitors, MAO-B inhibitors, other dopaminergic treatments (reason for discontinuation if applicable: inadequate response, adverse effects, other reason)
        - DBS, APO or Duodopa® [reason for discontinuation if applicable (inadequate response, adverse effects, other reason)].
    - Concomitant treatments (IMAO-A, non-selective IMAO, anticoagulant, anti-platelet, anti-emetic neuroleptic, immunosuppressant)
- Clinical assessment
    - Height, weight
    - General health status (Excellent, good, medium, bad)
    - Hoehn and Yahr staging
    - Schwab & England score
    - MDS-UPDRS subscores
    - Motor complications (motor fluctuations, dyskinesia, dystonia)
    - Levodopa-responsiveness test
- Other specific data
    - Contraindications to adrenergic treatments
    - Contraindications to perform a percutaneous endoscopic gastroscopy
    - Levodopa hypersensitivity
    - Carbidopa hypersensitivity
    - Apomorphin hypersensitivity
- Comorbidities
    - Uncontrolled cognitive and psychiatric disorders
        - Dementia, frontal lobe syndrome
        - Psychiatric disorders (Mental confusion, depression, psychotic disorders)
        - Behavioral disorders (behavioral instability, poor cooperation, family or social adaptive functioning disorders)

- Narrow-angle glaucoma
- Cardiovascular diseases
  - Heart failure
  - Severe cardiac arrhythmia
  - Acute stroke
  - Unstable angina
  - Uncontrolled hypertension
  - Severe cerebral macroangiopathy
- Hepatic impairment
- Respiratory failure
- Uncontrolled diabetes
- Kidney failure
- Melanoma history or suspicious undiagnosed skin lesions
- Pathology responsible for immunosuppression
- Progressive cancer or other life-threatening disease
- Pseudo-bulbar affect after PD surgery

- Advanced PD criteria according to Delphi method: motor symptom indicators, non-motor symptom indicators, function indicators

9. Event Reporting

This study is a non-interventional study and does not fall into the regulatory framework of biomedical research on medicinal products.

Under these conditions, the reporting of adverse events is subject to law 2011-2012 of 29 December 2011, related to the reinforcement of medicinal and Health product safety, and more particularly to article L 521-25 stating that any Healthcare professional, i.e. physician, dentist, midwife, nurse, pharmacist aware of any adverse event suspected to be due to a medicinal or Health product, including when associated with overdose, misuse, abuse, medication error, should report them immediately to the regional drug safety monitoring center (CRPV in France) in their area.

Good Pharmacovigilance Practices guidelines (29 August 2011) also strongly advise Health professionals to report any situation having potential or confirmed harmful effects on health or any other effect they consider necessary to declare to their local drug monitoring center, including the following situations even if not associated with any adverse event:

- overdose,
- exposure during pregnancy (including paternal exposure via semen) and breastfeeding,
- lack or loss of efficacy,
- occupational or inadvertent exposure,
- misuse,
- abuse,
- drug-drug or drug-food interactions,
- medication error,
- off label use,
- suspected transmission of any infectious agent,
- unexpected therapeutic or clinical benefit from use of the product.

In this epidemiological study, when a serious or non-serious adverse reaction or any of the situations above is observed with an AbbVie product (see list of AbbVie products in Appendix 2), physicians should report it to AbbVie Pharmacovigilance department (see contact details below) within 24 hours of awareness of the event (specifying whether a similar report has been sent to the regional drug safety monitoring center and the name of this study)

AbbVie Pharmacovigilance department
For any AbbVie product (except Duodopa®[redacted]
For Duodopa® : [redacted]

Product Complaints

A Product Complaint is any Complaint related to the biologic or drug component of any AbbVie product or to an AbbVie medical device component(s).
For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in

the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Product Complaints concerning any AbbVie product and/or device must be reported to AbbVie within 24 hours of the site's knowledge of the event via local Product Complaint reporting practices. The relevant AbbVie contact details for Product Complaint are specified below:

- For any AbbVie product (except for Duodopa®):

[redacted]

- For Duodopa®

[redacted]

[redacted]

10. Ethics and Quality

10.1 Regulatory Issues

The procedures described within the protocol regarding the conduct, assessment and documentation of the study are defined so that AbbVie and the participating physician respect the ethical principles of the 18th World Medical Association (Helsinki, Finland, 1964) amended by the 29th (Tokyo, Japan 1975), 35th (Venice, Italy, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, Scotland, 2000), 53rd (Washington, USA, 2002), 55th (Tokyo, Japan, 2004) and 59th (Seoul, Korea, 2008) General Assemblies.

This non interventional study will be conducted in accordance with:

- the recommendations of the professional code of ethics and with the guidelines of Good Pharmacoepidemiology Practices established by the *Association Des Epidémiologistes de Langue Française* (ADELF 2007)
- the articles L1121-1 and following of French Public Health Code
- the sections L.4113-6 and L.4113-9 of the French Public Health Code
- the law of January 6th 1978 addressing computing, files and personal information, amended by the law of July 1st 1994 and completed by the implementing decree of May 9th 1995 and Decree n° 2016-1537 dated on November 16, 2016.

10.2 Responsibility and Insurance by AbbVie

In accordance with the French legislation regarding studies not falling into the scope of interventional researches involving human persons, insurance is not required for this study.

10.3 Submission of the Study Protocol and Contract

Before the start of the study, the protocol, Patient Information and all other documents will be submitted to the relevant authorities, in compliance with French legislation.

The contracts will be submitted to the French National Medical Council (*Conseil National de l'Ordre des Médecins, CNOM*) before the study is implemented, in application of article L.4113-6 of the French Public Health Code and the interministerial circular letter dated July 9, 1993 (government gazette dated August 6, 1993).

Data on the financial agreement signed by the physicians with AbbVie, will be made public by AbbVie, in accordance with the Law on transparency (2011-2012 Law of December 29, 2011) and in application of Decree No. 2013-414 of May 21, 2013.

Before including the first patient, all legal and ethical obligations will be met. The study will comply with the methodology of reference MR-003.

10.4 Protocol Amendments

After the start of the study, amendments can be done and changes become an integral part of the study protocol.
Relevant authorities will be informed about any further amendment to the study protocol, in accordance with the French legislation.

10.5 Participant Confidentiality

In the CENSUS, no indirect or direct nominative data will be collected on individual patients as only weekly counts will be collected.

In the CORE descriptive part of the study, indirect nominative data of patients will be collected in accordance with the law of January 6th 1978 addressing computing, files and personal information, amended by the law of July 1st 1994 and completed by the implementing decree of May 9th 1995 and Decree n° 2016-1537 dated on November 16, 2016.

The patients' name will never be conveyed to AbbVie. Only patient number will appear on eCRF. If the name of the patient is included on another document, it will be masked before this document is supplied to AbbVie.

Patients (or legal representatives) will be also informed that all this information will be processed in the strict respect of confidentiality and professional secrecy.

The physician will keep a list of codes to identify patients and their medical records. This list will never be conveyed to AbbVie.

10.6 Patient Information

Before the inclusion in the CORE part of the study, the patient (or his/her legal representative) should be informed by the physician, in a comprehensive form, about the nature and purpose of this data collection. As only data available in medical records will be collected and as no additional diagnostic or monitoring procedures will be applied to the patients outside of routine clinical practice, the participation in the study does not convey any risks or burdens for the patient. However, patients (or legal representatives) will be provided with information about the study context. AbbVie will provide specific Patient Information Forms, in language readily understood by the patients or legal representatives.

10.7 Data Collection

Each center will document patient data in eCRFs. Examinations, diagnostic measures, findings and observations routinely performed on PD patients in medical practice will be entered by the

participating neurologist or staff under his/her supervision into the eCRFs provided by AbbVie, according to the research plan.
Only data specified in the research plan will be submitted to the data management center.

11. Data Management

The data management for this non-interventional study will be performed by a CRO under the supervision of AbbVie.

For data capture and data management of this study, a specific web-based eCRF will be employed.
The eCRF will include online validation during data capture, e.g. check on range, medical plausibility, typing errors. In addition to the system based plausibility checks, a formal query process will be implemented to solve inconsistencies in documented data. Electronic data queries will be created for discrepancies and missing values and displayed to the participating center via the eCRF system. The participating physician is required to respond promptly to queries and to make any necessary changes to the data.

Any correction or modification will be maintained in the Electronic Data Capture system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

At the end of the study, the participating physician will receive patient data for his or her center in a readable format on a compact disc that must be kept with the study records.

12. Data Analysis Plan

12.1 General Statistical Method

The statistical analysis plan (SAP) will be finalized before the data base lock.
The statistical analysis will be performed by a CRO under the supervision of AbbVie using the SAS® software (SAS Institute, North Carolina, USA) version 9.2 (or higher) on Windows™.

- **Descriptive statistical analysis**

A descriptive statistical analysis will be conducted on all the collected data, on the overall population and by sub-group granted that the sample size is not too small in each sub-group.

- Quantitative variables will be described by the following summary statistics: sample size (data provided, missing values), mean, standard deviation, median, mode if relevant (i.e. in case of a discrete variable), first and third quartiles and range (i.e. minimum and maximum observed values). If relevant, 95% confidence interval (CI) will be presented.
- Qualitative variables will be described using the number of non-missing values, the number of missing values, the frequency and percentage per modality. Note that missing values will be excluded from the calculation of percentages, unless their proportion is important (i.e. >10%). If relevant, 95% CI of the proportion will be presented.

The 95% confidence intervals will be calculated for all the endpoints.

The number of missing values for each variable will be reported. The proportion of missing values is expected to be low and randomly distributed. To the extent that there is no universally accepted method, no imputation procedure or replacement of missing data will be applied.

- **Statistical adjustments to correct for potential duplicates**

Some adjustments will be needed on the CENSUS patients' population to take into account of potential duplicates of:

- Patients who visit their neurologist many times over the 6-month study period. In this case, the number of medical visits per year collected in the Census form will be used to count each of these patients only once.
- Patients followed up by more than one neurologist who participates in the study and registered by all of them. The number of patients seen by another neurologist (data collected in the Census form) will be used to perform a sensitivity analysis. A conservative scenario will remove such patients (underestimation) and an alternative scenario will keep them (overestimation).

Potential duplicates will be also searched within the CORE patients population (due to the study duration, neurologists may fulfill many times an inclusion form for the same advanced PD outpatient). At the data management step, these duplicates will be detected within the clinical database and removed, on the basis of patients' combined indirect nominative data (age, gender, and date of initial PD diagnosis).

- **Statistical adjustments to correct for incompleteness of CENSUS reports**

CENSUS data require also corrective actions in case of:

- Non-completion of some weekly reports over the 6-month study period. The real number of weekly reports completed by a participating neurologist will be taken into account for extrapolations, subject to having a minimal number of assessable weekly reports (the threshold will be defined in the SAP).
- No return of any weekly CENSUS form. This missing information will be estimated using the number of advanced PD patients seen as outpatients in 2016 by the concerned neurologist.

- **Statistical adjustments to correct for non-inclusion of eligible patients**

Non-inclusion in the CORE part of the study of eligible advanced PD patients can happen in case of patient refusal, neurologist omission to propose the study or when the participating neurologist has reached the maximum threshold of recruitment (10 patients) before the end of the 6-month study period. The number of non-included eligible patients will be collected in the CENSUS weekly reports, and all the populations' estimates will be adjusted on this basis. The underlying assumption will be that non-included eligible patients do not differ significantly from included patients.

- **Statistical extrapolations to ensure generalizability**

First, the estimations will be made on a "raw" dataset, i.e. no extrapolation factor will be applied. As such, they will not be generalized to a one year activity of the observed neurologists and the targeted prescribers and consequently the Metropolitan French population of advanced PD patients.

In a second step, the results will be weighted first according to the parameters collected in the CENSUS, to extrapolate the information collected by each participating neurologist on a 6-month period to a full year of activity. Another optional weighting will be performed if it turns out that the distribution by stratum (type of activity and geographical distribution) of the sample of participating neurologists is significantly different from the distribution of Metropolitan French neurologists. And a last adjustment will be required to address the case of contacted neurologists refusing to participate because of no management of advanced PD patients. The weighting factors calculated will allow the results to accurately reflect the Metropolitan French population of advanced PD patients.

The first weighting factors/coefficients will include two components based on:

- The mean annual frequency of consultations of advanced PD patients with the participating neurologist
- The level of activity of the participating neurologists, estimated through the number of registered patients in the CENSUS and the duration of the associated reporting phase (through the dates of beginning and end of the CENSUS period, in the case of CENSUS duration will last less than 6 months without interruption for some neurologists and/or the cumulative length of the completed weekly CENSUS forms in the case of early discontinuations).

Consequently, the patient-dependent component will assess the mean weight of the patient considered in all consultations performed annually by his/her neurologist. The more a patient

consults his/her neurologist, the lower his/her representativeness. The neurologist-dependent component will assess the average weight of a participating neurologist in the recruitment of patients of the study (all neurologists will be put to the same level according to the duration of their Census). This weight will be applied to each patient included by the observed neurologist and will reflect the number of individuals represented by each recruited patient in the targeted population based on the level of activity of this neurologist.

The optional weighting factors will use the observed strata-distribution of participating neurologists and the reference distribution calculated from a national updated database comprising all the neurologists currently active and not retired at the time of the study in Metropolitan France.
The last weighting factors will rely on the number of physicians refusing to participate due to a lack of advanced PD patients per stratum.

12.2 Analysis Physician Population

Physicians' population will be analyzed by subgroups of physician's type of practice per phone area, and on the overall sample.

The following different cases of physicians will be distinguished and analyzed:

- Targeted physicians: physicians on the IMS OneKey list who are planned to be contacted (n=2611) during the recruitment step
- Contacted physicians: physicians who have been reached out by phone and gave a yes/no answer
- Physicians who agreed to participate: physicians willing to participate in this study
- Physicians who refused to participate and reason(s) for refusal, including lack of advanced PD patients. Specialists refusing to participate because of no management of such patients will be specifically counted
- Physicians with effective participation: physicians with at least one weekly CENSUS form completed over the 6-month study period.

The physicians' participation will be examined via different ratios:

- Contact rate = contacted physicians / targeted physicians
- Response rate = physicians who agreed to participate / contacted physicians
- Refusal rate = 1 – response rate
- Effective participation rate (or cooperation rate) = physicians with effective participation / physicians who agreed to participate.

Moreover, missing and/or non-analyzable eCRFs (weekly CENSUS forms and CORE study questionnaires) will be detected and counted:

- Estimation of the percentage of physicians who did not return any weekly CENSUS form over the 6-month study period
- Estimation of the percentage of physicians with non-completion of some weekly CENSUS forms over the 6-month study period, and summary of the number of missing weeks for these physicians (mean, std, median, Q1-Q3, min, max)

- Estimation of the percentage of physicians who did not include any patient in the CORE study
- Estimation of the percentage of physicians with incomplete CORE questionnaires (key data).

To evaluate the representativeness of the physicians' sample, distribution per strata of the effective participating neurologists will be retrospectively compared to the source population, i.e. practicing neurologists in Metropolitan France. If significant differences are observed, adjustments will be performed. The weighting/adjustment methods to correct for targeted physicians without advanced PD patients, missing CENSUS forms, sample deviations will be specified in the SAP.
The mean number of recruited patients per effective participating physician will also be calculated.
The sample of effective participating physicians will be described per type of practice and in terms of all characteristics collected.

12.3 Analysis Patient Populations

The general statistical considerations described above (§12.1) will be applied for quantitative and qualitative variables. Confidence intervals of 95% will be calculated for endpoints.
Two distinct patient populations will be considered: CENSUS patient population and CORE patient population. Another sub-population will be of interest: patients from the CENSUS population eligible for the CORE part of the study but not included in this part. Note that only the size of this sub-population will be provided according to the reason of non-participation [patient refusal, maximum threshold of recruitment reached at the site (10 patients), neurologist omission to propose the study, other reason].
Among these populations, collected data will be analyzed by subgroups of patients according to the type of center visited (hospital-based physician / private center / physician with mixed practice), and on the overall dataset.

12.4 Endpoints

12.4.1 Primary Endpoint

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.

Intermediate endpoints will be defined as follows:

1. Number and percentage of patients not eligible for Deep Brain Stimulation
2. Number and percentage of patients presenting contra-indication, intolerance or failure to subcutaneous apomorphine continuous infusion
3. Number and percentage of patients without contra-indications and precautions for Duodopa® use as they are defined in the drug SmPC (ANSM, Duodopa®).

These three intermediate endpoints will be first estimated separately and then their combination will be considered. To provide a synthetic criterion summarizing these three main points per advanced PD patient, the number of times a patient fulfills the conditions will be counted. Then, the percentage of patients who fulfill the defined conditions on 3 points out of 3 will be evaluated

(patients with complete eligibility). In the same way, the percentage of patients who meet the defined conditions at 2 (respectively 1, 0) points out of 3 will be estimated.
Moreover, the profile of patients with complete eligibility to these three main points could be identified and described with all available relevant covariates collected in the CORE part of the study.
In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' and patients' universe. In a second step, the results will be weighted / adjusted in order to accurately reflect the population that the study seeks to measure.

12.4.2 Secondary Endpoints

- **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.**

The third intermediate endpoint defined for the primary objective will be used to establish this population.

- **To describe advanced PD patients and disease characteristics (including background history).**

The data collected in the CORE descriptive part of the study will allow to:

- Characterize the profile of patients with advanced PD:
  - Sociodemographic data (age, gender)
  - Disease history
  - Clinical assessment (at inclusion)

- Describe the treatment history of patients with advanced PD:
  - PD prior and ongoing treatments
  - Concomitant treatments

Both calculations performed on raw data and weighted / adjusted results will be provided.

- **To estimate the proportion of PD patients eligible for each invasive therapy (DBS, APO or Duodopa®).**

The data collected in the CORE descriptive part of the study will allow to estimate:

- The number and percentage of eligible patients to each invasive treatment (DBS, APO or Duodopa®), in all and per invasive therapy defined by the absence of contra-indications for any of the 3 therapeutic alternatives.

The contra-indications for DBS will be those specified in the CNEDiMTS opinion. The last published one will be used as reference (HAS, CNEDiMTS opinion, Vercise®, 2015). The indication, contra-indications and precautions for use of APO will be those defined in the apomorphine SmPC (ANSM, Apokinon®).

Group size of eligible patients to each invasive treatment is going to be derived after all data are collected. Both calculations performed on raw data and weighted / adjusted results will be provided.

12.4.3 Exploratory Objective

- **To estimate the size of the population of PD patients eligible for Duodopa® when advanced PD criteria are defined by Delphi method.**

The following endpoints will be defined:

- Regarding the top 3 clinically relevant most important motor symptom indicators:
  - Number and percentage of patients with moderate level of troublesome motor fluctuations
  - Number and percentage of patients with at least 2 hours of the day with off-symptoms
  - Number and percentage of patients with at least 1 hour of the day with troublesome dyskinesia
  - Number and percentage of patients with none /1/2/3 of the above indicators
- Regarding the top 3 clinically relevant most important non-motor symptom indicators:
  - Number and percentage of patients with mild level of dementia
  - Number and percentage of patients with non-transitory troublesome hallucinations
  - Number and percentage of patients with moderate level of psychosis
  - Number and percentage of patients with none /1/2/3 of the above indicators
- Regarding the top 3 clinically relevant most important function indicators:
  - Number and percentage of patients with repeated falls despite optimal treatment
  - Number and percentage of patients needing help with activities of daily living at least some of the time
  - Number and percentage of patients who are not being able to perform complex tasks – most of the time
  - Number and percentage of patients with none /1/2/3 of the above indicators
- Combination of the above three domains (motor symptom indicators / non-motor symptom indicators / function indicators).

These endpoints will be estimated among the complete dataset of included patients. Then they will be combined with the endpoints defining the eligibility to Duodopa®.

Both calculations performed on raw data and weighted / adjusted results will be provided.

12.4.4 Other Analysis

All other analyses that could give interesting information with respect of study objectives will be performed after agreement of the Scientific Committee of the study.
Additional details for potential other analysis will be specified in the SAP.

12.5 Sample Size Calculation

The primary objective of this study is to estimate, in Metropolitan France, the size of the population of PD patients eligible for Duodopa® according to the indication defined by the French Authority for Health in its Transparency Committee's opinion. In order to achieve this objective, it will be necessary to calculate the number of idiopathic patients with advanced PD seen in outpatient consultations by neurologists participating in the study and to estimate among these patients the proportion eligible for Duodopa®. This is the reason why the participating neurologists will first have to include in the Census phase all the advanced PD patients consecutively seen in consultation over the Census period. The duration of the data collection in the Census will be 6 months to ensure data exhaustiveness since PD patients are assessed by a neurologist at least every 6 months in routine medical practice.

For each practicing neurologist the proportion of patients with an advanced stage of the disease appears to be relatively low. To the best of our knowledge, there is no published data in a French context, with a similar definition of advanced disease to that of this study. Most of the time, insufficient response to antiparkinsonian medications is not clearly defined. Therefore, in accordance to experts' opinion, advanced disease will be defined by treatment duration with levodopa for at least 3 years considering that motor complications could occur from that moment, with presence of motor complications and lack of control of those complications under conventional antiparkinsonian treatment.

To estimate the population of advanced PD patients who would be eligible for Duodopa® according to the Transparency Committee, it will be necessary to count and identify all the patients who:

- Do not meet the eligibility criteria for DBS
- Present contra-indication, intolerance or treatment failure to APO
- And have no contraindication to Duodopa® or for the placement of a gastrointestinal tube.

Note that the additional condition for Duodopa® treatment suggested by the French Authority for Health in its last opinion for Duodopa® (acceptance of this therapy by the patient) could not be assessed directly in this study as it is not possible to ask neurologists to propose such a treatment to their patients in current medical practice only to meet the objectives of this non-interventional study.

The compliance to the above conditions, first taken separately and then simultaneously, will be verified among the patients included in the CORE descriptive part of the study. Moreover, this compliance associated with data from the Census will help achieve the main objective of the study by calculating ratios and their 95% confidence intervals (CI).

Determining the number of subjects required for the CORE descriptive part of the study is based on the level of precision needed to achieve in these estimates. The formula, based on a normal approximation to the binomial distribution is specified below. It helps to calculate the number of patients (n) required to estimate an unknown proportion (p) with a level of data accuracy (e) (Bouyer et al, 1995).

$$n = \frac{p.(1-p).(Z_{1-\alpha/2})^2}{e^2}$$

where "p" is the estimated proportion, "e" is the precision [one half the desired width of the CI], and "$Z_{1-\alpha/2}$" is the 1 – α/2 quantile of standard normal distribution.
The following table provides the margin of error expected for a 95% CI based on different values for the sample size (n) and the required proportion (p).

Table 3: Sample size required for different levels of precision and different values of the proportion

	Precisions for 95% CI						
Estimated proportion p	**10%**	**8%**	**6%**	**5%**	**4%**	**3%**	**2%**
10%	35	54	96	138	216	384	864
20%	61	96	171	246	384	683	1,537
30%	81	126	224	323	504	896	2,017
40%	92	144	256	369	576	1,024	2,305
50%	96	150	267	384	600	1,067	2,401
60%	92	144	256	369	576	1,024	2,305
70%	81	126	224	323	504	896	2,017
80%	61	96	171	246	384	683	1,537
90%	35	54	96	138	216	384	864

To the extent that the level of the estimated proportions is *a priori* unknown (no available data regarding the proportion of advanced PD patients who may be eligible for Duodopa® treatment in France), the worst case scenario for sample size calculation will be assumed with a proportion of 50% of advanced PD patients which might be eligible for Duodopa®. This conservative assumption leads to a larger sample size. The actual proportion will most likely be smaller than 50%. In such case, the half width of 95% CI will be smaller than 5%, which means a higher precision could be achieved.

Considering this hypothesis and in order to achieve a 95% CI with a margin of error of +/- 5% on either side of the estimated proportion, a total of 384 patients included in the CORE descriptive part of the study is required.

In order to take into account non-assessable patients (estimated at 15% of all patients included in the CORE descriptive part of the study), a sample of 442 patients in this study part will be recruited by 289 neurologists (339 neurologists will be selected to consider the inactive neurologists, estimated at 15% of all the participating physicians).

No predefined number of inclusions will be asked per neurologist in the CORE descriptive part in order to take into account the real activity of each specialist. For 289 active neurologists at a maximum and a total 442 inclusions as expected, a mean of 1.5 advanced PD patients will be include in each center, which will allow the participation of all types of neurologists. However, to avoid a potential center-effect and to allow the participation of the neurologists least involved in advanced PD patients management, a maximum number of inclusions will be fixed per center (n=10).

13. Limitations of the Research Methods

In order to be able to extrapolate the study results to the entire population of advanced PD patients eligible for Duodopa®, potential sources of bias in the study must be identified concurrently and controlled as far as possible.

In particular, this epidemiological study should answer to the reservations expressed by the Transparency Committee (Duodopa® Transparency Committee opinion, 2013) regarding the reevaluation of the French target population of Duodopa® proposed by AbbVie in 2013:

- Questioning about the definition of advanced PD for data extracted from the PMSI
- Questioning about the definition of patients eligible for Duodopa® therapy and number of participating centers in DUOCIBLE.

Since EPI PARK is a cross-sectional study, the description of studied parameters could be subject to a selection bias at the time of recruitment in terms of the studied populations.
Regarding the primary criterion of the study (estimate of population of advanced PD patients eligible for Duodopa® in accordance with the conditions defined by the French Authority for Health in its Transparency Committee's opinion),

- The source population of physicians should be representative of the target population (physicians involved in advanced PD management)
- The population of the participating physicians should be representative of the target population
- The population of patients registered in the CENSUS part of the study by the participating physicians should be as exhaustively as possible
- The population of patients included in the CORE descriptive CENSUS part of the study should be representative of the population of advanced PD patients.

13.1 Control Measures for Centers

Following concurrent and retrospective control measures will be implemented over the CENSUS study period:

- According to recommendations published by the French Authority for Health (HAS 2014), the PD diagnosis should be confirmed by a neurologist and every 6-month assessment should be performed by such specialist. General practitioners may ensure patients' follow-up and treatment renewal only. This epidemiological study conducted with neurologists over a 6-month period should then ensure to target all the required population
- A national updated database comprising all the neurologists practicing in Metropolitan France (n=2,611), provided by a Company independent from the sponsor (IMS Health) will be used for physicians' recruitment which will be performed without any involvement of the Sponsor
- Using this national database, neurologists will be randomly solicited to participate in the study on the basis of a quotas' method taking into account the more relevant criteria regarding study objectives. A total of 15 strata will be defined (3 types of medical practice x 5

geographic locations) with a predetermined number of neurologists to recruit in each stratum

- Since the neurologists who are the less involved in advanced PD patients' management may be the less interested to participate, specialists refusing to participate because of no management of such patients will be specifically counted per stratum during the recruitment. Estimations of the sizes of populations will be adjusted on this basis
- The method of neurologists' recruitment and the wide number of selected centers (n=339) will ensure that neurologists with low involvement in a PD treatment implementation (non-Movement Disorder Expert centers for PD and neurologists with private practice) will participate in the study
- The population of active centers will be retrospectively compared to the source population, according to predefined strata to be applied. In case of significant differences, adjustments will be performed.

13.2 Control Measures for Patients

The following concurrent and retrospective control measures will be implemented over the **CENSUS** study period:

- The number of patients being registered in the 2013 health care system database as being affected by PD was assessed at 195,200 for France with overseas territories and at 191,500 for Metropolitan France (SG/DGOS 2015). Registration of all advanced and non-advanced PD outpatients in the CENSUS may have allowed to contrast the extrapolated population of PD patients in the study with this estimation. However, considering the study duration (a 6-month period), it appears unreasonable to ask neurologists to register all their PD patients (with advanced disease or not), in particular for Movement Disorder Expert centers over such a duration, at the risk of insufficient collected weeks forms for valid calculations and extrapolations
- As no current consensus exists for the definition of advanced PD, the study Scientific Committee comprising two Movement Disorder Expert centers for PD (see Section Appendix 1) retained a wide enough definition to cover all the patients who could benefit from one of the three invasive therapies (DBS, APO or Duodopa®)
- Over the 6-month study period, neurologists will be asked to count relevant patients on a weekly basis to limit the recall bias over such a period. Weekly reports should be completed even if no advanced PD patient is seen, using a specific question (advanced PD patients seen over this week: Yes/ No)
- Data will be captured by neurologists on a eCRF that will allow immediate automatic (e)mail reminders completed if needed by phone calls in the case of non-completion of weekly forms. In case of non-completion of some reports over the 6-month period, the real number of weekly reports completed will be taken into account for extrapolations
- Among the neurologists having agreed to participate in the study, an adjustment will be applied for those who did not return any weekly CENSUS form, on the basis of the number of advanced PD patients they saw as outpatients in 2016. However, cautions will have to be taken because this number may be only declarative in some centers

- Considering the study duration (6 months), neurologists may count many times the same advanced PD outpatient in the CENSUS. They will be then asked to specify in their weekly reports the number of yearly medical visits for advanced PD patients (number of patients with 1, 2, 3, 4 or more yearly visits). The taking into account of these potential duplicates (on the basis of the number of weekly CENSUS forms completed by each participating neurologist) aims to limit a potential overestimation of the population of advanced PD patients
- Several advanced PD patients may be followed up by a neurologist other than the one who will complete the weekly reports while these other neurologists will participate in the study or not. Participating neurologists will be then asked to specify in their weekly reports the number of patients seen by another neurologist. Removal of these potential duplicates will be applied for final calculations. Since this conservative measure (assumption: all the duplicates are counted in the completed CENSUS weekly reports of the study) may lead to underestimates, a sensitivity analysis will be performed without taking into account this parameter
- The number of non-included eligible advanced PD patients will be collected in the weekly reports and the populations' estimates will be adjusted on this basis, assuming that such patients are representative of the overall population of advanced PD patients. Due to the shortness of the CENSUS form, the absence of selection bias between patients who were actually included in the CORE part of the study and all eligible patients who could have been (e.g. patients not included due to patient refusal, maximum threshold of recruitment reached in the CORE part,…) could not be checked.

Regarding the concomitant **CORE** descriptive part of the study, following concurrent and retrospective control measures will be implemented:

- Since late stage PD symptoms could include cognitive and psychotic problems, the inclusion of advanced PD patients may be limited by the impossibility for such patients to be informed about the study content and to sign the Informed Consent Form. To limit this selection bias which may lead to populations underestimation, legal representatives will be solicited for the participation of such patients
- Using the eCRF functions, inclusion forms will be automatically generated on the basis of the number of included advanced PD patients as specified in the weekly CENSUS forms completed by each neurologist. Phone calls and/or (e)mails reminders will be performed in the case of data not captured by the specialists for these patients, unless the threshold of 10 patients was already reached
- To limit a potential 'center effect', the number of included patients per neurologist will be limited (10 advanced PD patients). Assuming that patients included in these centers will be representative to all the advanced PD patients they will manage over the 6-month study period, adjustments will be performed on the basis of the number of advanced PD outpatients registered in the CENSUS. Consequently, the mean number of included advanced PD patients expected per center will vary from 1 to 10 (i.e. 1 to 2 in mean considering all the active centers in the study)
- Considering the study duration (6 months), neurologists may complete many times an inclusion form for the same advanced PD outpatient. After the end of data collection,

potential duplicates will be searched within the clinical database and removed, on the basis of patients' combined indirect nominative data (age, gender, date of initial PD diagnosis,…)

- Considering the study duration (6 months), the same advanced PD outpatient might be seen many times by the same participating physician or by distinct participating physicians. Such a patient might decline to participate the first time and give his/her agreement to the following visit. These are undetectable and incorrigible cases that are expected very scarce.

14. Final Report and Publications

At the end of the medical Research study, a report or publication will be written by AbbVie. This report/publication will contain a description of the objectives of the study, the methodology and its results and conclusions. The completed Data Recording Forms, questionnaires and the final study output are the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without the express written approval from AbbVie.

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16. Research Plan Signature Page

AbbVie

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EPI PARK

Advanced Parkinson's disease treatment eligibility in France: an epidemiological study.

17. Appendices

Appendix 1: Scientific Committee

[redacted]

Appendix 2 : List of AbbVie products

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Annexe

TITRE : LISTE DES MEDICAMENTS A INTERET THERAPEUTIQUE MAJEUR COMMERCIALISES PAR ABBVIE, EN FRANCE

Référence : ANX-ABV-PHA-007 / 5 [redacted] / Date de création : 16/03/2015 Domaine : Affaires Pharmaceutiques

	Médicaments	Substance active
1.	DUODOPA 20 mg/ml + 5 mg/ml, gel intestinal	Lévodopa, carbidopa
2.	EXVIERA 250mg, comprimé pelliculé	Dasabuvir
3.	HUMIRA 40 mg, solution injectable en seringue préremplie	Adalimumab
4.	HUMIRA 40 mg, solution injectable en stylo prérempli	Adalimumab
5.	HUMIRA 40 mg/0,8 ml, solution injectable pour usage pédiatrique (en flacon)	Adalimumab
6.	KALETRA 100 mg/25 mg, comprimé pelliculé	Lopinavir, ritonavir
7.	KALETRA 200 mg/50 mg, comprimé pelliculé	Lopinavir, ritonavir
8.	KALETRA (80 mg + 20 mg) / ml, solution buvable	Lopinavir, ritonavir
9.	NORVIR 100 mg, comprimé pelliculé	Ritonavir
10.	NORVIR 80 mg/ml, solution buvable	Ritonavir
11.	SEVORANE, liquide pour inhalation par vapeur	Sévoflurane
12.	SYNAGIS 100 mg, poudre et solvant pour solution injectable	Palivizumab
13.	SYNAGIS 50 mg, poudre et solvant pour solution injectable	Palivizumab
14.	VIEKIRAX 12,5 mg/ 75 mg/ 50 mg, comprimé pelliculé	Ombitasvir/Paritaprévir/Ritonavir

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Annexe

TITRE : LISTE DES DISPOSITIFS MEDICAUX - DUODOPA 20 MG/ML + 5 MG/ML, GEL INTESTINAL

Référence : ANX-ABV-PHA-006 / 4 [redacted]

Domaine : Affaires Pharmaceutiques
Date de création : 06/10/2016

Dénomination usuelle	Classe	Fabricant
Pompe		
Pompe CADD-Legacy Duodopa	IIb	Smiths Medical
Cache de protection (*)	-	SIMS Deltec
Couvercle du compartiment à pile (*)	-	SIMS Deltec
Câble optionnel de dose supplémentaire	IIb	SIMS Deltec
Clé pour la pompe (*) avec logo	-	--
Matériel de la Phase Naso-Intestinale		
Sonde d'alimentation naso-gastrique Kangaroo Covidien	IIa	Covidien
Prolongateur Vygon 20 cm	IIa	Vygon
Prolongateur Vygon 50 cm	IIa	Vygon
Adaptateur Vygon	I stérile	Vygon
Matériel de la Phase Gastro-Intestinale		
Dispositif Gastro-Intestinal BOSTON		
Kit standard GEP FR 20 - EndoVive	IIb	Boston Scientific
Kit de Tube d'alimentation jéjunal 80 cm (sonde intestinale)	IIb	Boston Scientific
Kit de Tube d'alimentation jéjunal 105 cm (sonde intestinale)	IIb	Boston Scientific
Bouchon pour sonde J	IIb	Boston Scientific
Dispositif Gastro-Intestinal FREKA		
FREKA GEP (**) Kit Gastrique FR 15 (35 cm)	IIb	Fresenius Kabi AG
FREKA Kit de Sonde intestinale FR 9 pour GEP (**) FR 15 (sonde intestinale)	IIb	Fresenius Kabi AG
Dispositif Gastro-Intestinal AbbVie		
Kit de Sonde de GEP (**) 15 FR	IIb	AbbVie
Kit de Sonde de GEP (**) 20 FR	IIb	AbbVie
Sonde intestinale 9 FR	IIb	AbbVie
Connecteurs BOSTON		
Adaptateur de rinçage	IIb	Boston Scientific
Connecteurs FREKA		
Connecteur de rinçage femelle/femelle pour seringue (bleu)	I	Fresenius Kabi AG
FREKA Adapteur Y	I	Fresenius Kabi AG
Adaptateur click FREKA vert FR 9 / GEP (**) FR 15	I	Fresenius Kabi AG
Plaque de fixation externe pour FREKA GEP (**) FR 15	I	Fresenius Kabi AG

[redacted]

Dénomination usuelle	Classe	Fabricant
Connecteurs AbbVie		
Adaptateur click pour sonde intestinale 9 FR	I	AbbVie
Adaptateur pour seringue luer AbbVie	I	AbbVie
Connecteur en Y pour sonde de GEP 15 FR	I	AbbVie
Connecteur en Y pour sonde de GEP 20 FR	I stérile	AbbVie
Plaque de rétention pour sonde de GEP 15 FR	I	AbbVie
Plaque de rétention pour sonde de GEP 20 FR	I	AbbVie
Connecteurs NUTRICIA		
Combifix Adaptateur double femelle/femelle (***) (connecteur de rinçage)	I stérile	B/BRAUN
Dispositifs de Port AbbVie		
Pochette – bandoulière	I	AbbVie
Pochette – ceinture	I	AbbVie

(*) Accessoire
(**) Gastrostomie Endoscopique Percutanée
(***) Ce dispositif n'est plus distribué