Title Page

Title	**COSMOS - CO**medication **S**tudy assessing **M**ono- and c**O**mbination therapy with levodopa-carbidopa inte**S**tinal gel (P16-831)
Protocol Version Identifier	Original Protocol
Date of Last Version of Protocol	14th June 2017
EU PAS Register Number	Study not registered
Active Substance	Not applicable
Medicinal Product	Not applicable
Product Reference	Not applicable
Procedure Number	Not applicable
Marketing Authorisation Holder(s)	EU AbbVie Ltd. Vanwall Road Maidenhead Berkshire SL6 4XE United Kingdom
Joint PASS	Not applicable
Research Question and Objectives	The primary objective of this multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) is to evaluate the percentages of Advanced PD patients on LCIG monotherapy right after LCIG initiation and at 3, 6, 9, and 12 months, respectively. The secondary objectives are • To describe PD medication management, and the main reasons justifying their use, directly prior to LCIG initiation, at LCIG initiation and during long-term LCIG treatment • To describe LCIG infusion settings and substantial dose adjustments (section 9.2.7.7) and the respective reasons • To describe the Healthcare Resource Utilization (HCRU) • To identify the physician's and patient's/caregiver's overall preference for the pharmacological treatment approach using LCIG as monotherapy (section 9.2.7.7) vs. LCIG plus add-on PD medication • To identify predictors for achieving long-term monotherapy (section 9.2.7.7) with LCIG vs. LCIG plus add-on PD medication, based on the patient's profile and the physician's profile

	• To describe the latency from LCIG initiation until LCIG is given as a monotherapy and the average duration of LCIG monotherapy. • To describe the latency from the initiation of LCIG therapy until the introduction or tapering of each PD medication, or until substantial dose adjustments of LCIG • To investigate all of the above objectives for the participating countries who have enrolled a minimum of 20 study subjects
Country(-ies) of Study	Approximately 15 countries in Europe (Austria, Bulgaria, Croatia, Romania, Czech Republic, Estonia, Hungary, Ireland, Germany, Netherlands, Slovakia and Spain), Canada and Australia, among others; final list of participating countries to be confirmed
Author	GMA and ad hoc functions

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	EU AbbVie Ltd. Vanwall Road Maidenhead Berkshire SL6 4XE United Kingdom
MAH Contact Person	Not applicable

1.0 Table of Contents

2.0 Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
APD	Advanced Parkinson's disease
AUDD	Authorization for Use and Disclosure of Data
BMQ	Beliefs medication questionnaire
DBS	Deep Brain Stimulation
CDD	Continuous Drug Delivery
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CSAI	Continuous sub-cutaneous apomorphine infusion
eCRF	Electronic Case Report Form
HCRU	Healthcare Resource Utilization
ICF	Informed Consent Form
IRB	Institutional Review Board
LCIG	Levodopa-Carbidopa Intestinal Gel
LD	Levodopa
LEDD	Levodopa equivalent daily dosage
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Metal State Examination
NMSS	Non-Motor Symptom Scale
PD	Parkinson's disease
PDQ-8	Parkinson's Disease Questionnaire-8
PDSS-2	Parkinson's Disease Sleep Scale-2
PEG-J	Percutaneous endoscopic gastrostomy- with jejunal extension
PC	Product Complaint
PLMS	Periodic Limb Movements of Sleep
PRO	Patient reported outcomes
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
REM	Rapid Eye Movement
RLS	Restless Legs Syndrome
SAE	Serious Adverse Event

UPDRS	Unified Parkinson's Disease Rating Scale

3.0 Responsible Parties

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4.0 Abstract

Title: COSMOS - COmedication **S**tudy assessing **M**ono- and c**O**mbination therapy with levodopa carbidopa inte**S**tinal gel

Rationale and Background: Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder with a worldwide estimated prevalence of 0.3% in the general population 40 years of age and older [1]. The most effective symptomatic therapy for PD remains levodopa, a precursor of dopamine. However, within several years of levodopa therapy initiation, a considerable number of patients develop complications, and after 5 to 10 years of treatment at least 50% of patients develop motor fluctuations and abnormal involuntary movements (dyskinesia).

As PD progresses, even complex oral drug regimens may become insufficient for symptom control [2]. Therefore, other therapeutic strategies have been developed, including treatments based on continuous drug delivery (CDD) [3-5].

Among the enteric CDD formulations, levodopa-carbidopa intestinal gel (LCIG) is the only formulation of levodopa and carbidopa which has been found to be suitable for continuous long-term intestinal infusion so far.

LCIG (Duodopa®) appears to possess the potential to be used as monotherapy in many patients, or at least enable significant reductions of the add-on PD medication. Thereby, LCIG may achieve a much-needed simplification of the treatment regimen, allowing for a reduction of detrimental drug-drug interactions (DDI) [6].

So far, data on patients in whom LCIG monotherapy or significant reductions of add-on PD medication was achieved, have been derived from two clinical studies with rigorous protocols [7, 8], and therefore cannot be easily translated into routine clinical practice. Also, recent observational studies demonstrated overall varying approaches in the management of add-on PD medications in routine clinical practice before and after initiation of LCIG treatment [9, 10].

In a multinational registry on the efficacy and safety of LCIG in routine care (GLORIA registry), 36-40% of APD patients were treated over 24 months with LCIG monotherapy (without any additional oral PD medication); however no background information on the rationale for the use of add-on PD medication (e.g., introduction/tapering/maintenance) was collected [11].

In summary, no systematic, comprehensive and homogeneous real-world data are available – neither on LCIG monotherapy or LCIG in combination with add-on PD medication, nor on the management of add-on PD medications before or upon LCIG initiation, or during long-term LCIG maintenance therapy.

The present study attempts to fill this knowledge gap and generate relevant data from routine clinical practice on the usability of LCIG as a monotherapy and in combination with add-on PD medications. In addition, useful data on the handling of add-on PD medication (e.g. tapering, introduction) upon LCIG initiation and over long-term use shall be collected.

Research Question and Objectives: The primary objective of this multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) is to evaluate the percentages of Advanced PD patients on LCIG monotherapy right after LCIG initiation and at 3, 6, 9, and 12 months, respectively.

The secondary objectives are

- To describe PD medication management, and the main reasons justifying their use, directly prior to LCIG initiation, at LCIG initiation and during long-term LCIG treatment

- To describe LCIG infusion settings and substantial dose adjustments and the respective reasons
- To describe the Healthcare Resource Utilization (HCRU)
- To identify the physician's and patient's/caregiver's overall preference for the pharmacological treatment approach using LCIG as monotherapy vs. LCIG plus add-on PD medication
- To identify predictors for achieving long-term monotherapy with LCIG vs. LCIG plus add-on PD medication, based on the patient's profile and the physician's profile
- To describe the latency from LCIG initiation until LCIG is given as a monotherapy and the average duration of LCIG monotherapy.
- To describe the latency from the initiation of LCIG therapy until the introduction or tapering of each PD medication, or until substantial dose adjustments of LCIG
- To evaluate the percentage of patients who are on LCIG monotherapy, PD medication management and HCRU for the participating countries who have enrolled a minimum of 20 study subjects

Study Design: This is a multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) of patients with APD treated with LCIG in a routine clinical setting. Patients who are receiving LCIG according to the approved local product label and reimbursement guidelines will be asked to participate.

This study will include a retrospective section, collecting the below specified data from patient's medical records from the time of the decision to start LCIG treatment until the present day, and a single study visit (cross-sectional) with clinical status and subjective assessments of patients at present time.

Patients, who have received LCIG for at least 12 months, and who satisfy all the inclusion criteria and exclusion criteria will be eligible to be enrolled into this PMOS. All eligible LCIG patients will be included consecutively at each participating study site.

The primary endpoint of this PMOS will be the percentages of APD patients on LCIG monotherapy right after LCIG initiation (after permanent system placement) and at 3, 6, 9, and 12, respectively.

The secondary endpoints are:

- Descriptive data from patient's PD medication:
    - For add-on PD medication: percentage of patient on each PD medication (by drugs and class), total daily dose and levodopa equivalent Daily dose (LEDD) , posology (number of times per day);
    - For LCIG infusion settings and substantial dose adjustments: total dose per day and specific for each type of dose (morning dose and continuous dose) and number of hours of infusion.
    - Tapering process: number of days required for the tapering process, total dose per day and posology for add-on PD medication prior to LCIG initiation, at LCIG initiation (titration) or during ongoing LCIG treatment
    - Main reasons for introduction or tapering of add-on PD medication or LCIG substantial dose adjustments
- Latency and duration of treatments data:
    - Number of days or months from LCIG initiation until LCIG is given as a monotherapy and the duration of LCIG monotherapy.
    - Number of days or months from LCIG initiation until the introduction or tapering of each PD medication, or until any LCIG substantial dose adjustments.

- LCIG monotherapy vs LCIG plus add-on PD medication data:
  - Healthcare Resource Utilization, as measured by Healthcare Resource Utilization Questionnaire (HCRU)
  - Patient's, caregiver's, and physician's overall preference on LCIG monotherapy vs. LCIG plus add-on PD medication, percentage of patient's and physician's preference for each of the options
  - Predictors for LCIG as monotherapy vs. LCIG plus add-on PD medication based on the patient's profile, including socio-demographics , clinical status (motor and non-motor symptoms), Levodopa-equivalent dose (LED), PD medication and Quality of Life
  - Predictors for LCIG as monotherapy vs. LCIG plus add-on PD medications based on the physician's profile including experience as measured by, number of years on APD patient management, number of years using LCIG therapy, and number of patients on LCIG therapy

Population: Patients that may be enrolled in this study are adult patients with APD, who are under treatment with LCIG according to the local product label and specific reimbursement criteria. Decision to offer study participation has been made by their physician, based on meeting all of the inclusion criteria and none of the exclusion criteria.

A total of approximately 400 patients with APD will be included.

Patients must meet all of the following criteria:

1. Patients diagnosed with APD and on LCIG treatment for at least 12 months
2. Patients must have been on continuous LCIG treatment for at least 80% of days in the preceding year
3. Patients must be treated by the same physician (PI or co-investigator) since the initiation of LCIG.
4. Decision to treat with LCIG was made and therapy was started by the physician prior to any decision to approach the patient to participate in this study
5. Prior to any data collection, the patient, or legal authorized representative (LAR) has voluntarily signed an Authorization for Use/Disclosure of Data (AUDD)/informed consent form (ICF) according to national regulations after the study has been explained and the subject has had the opportunity to have questions answered

Patients must not be enrolled if they meet any of the following criteria:

1. Participation in a concurrent or a previous interventional clinical trial during which the patient was on LCIG therapy
2. Lack of motivation or insufficient language skills to complete the study questionnaires.

Variables: This is a PMOS with the objective of collecting data on the clinical practice of LCIG treatment upon treatment initiation and long-term follow-up.

Clinical Variables:

Information about the previous PD medication, and add-on PD medication and LCIG infusion settings will be retrospectively collected from patient`s medical records.

Actual Parkinson's disease status and motor symptoms/motor complications will be measured using the following tools:

- Duration of OFF time and dyskinesia (hours during the day prior to the clinical visit) as reported by the patient
- UPDRS Parts III (motor evaluation) and IV (Treatment complication)

The following health outcomes will be measured using the following tools:

- UPDRS Part I (evaluation of mentation, behavior, and mood)
- UPDRS Part II (self-evaluation of the activities of daily living (ADLs))
- UPDRS Part V (Modified Hoehn and Yahr stage of severity of Parkinson's disease)
- PDQ-8 (Parkinson Disease Questionnaire) to evaluate PD patient's quality of life.

Non-motor symptoms including specific tool for sleep/daytime sleepiness, impulse control disorders and mental status will be measured using the following tools:

- Non-motor Symptoms Scale (NMSS)
- Parkinson´s Disease Sleep Scale-2 (PDSS-2)
- Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease- Rating Scale (QUIP-RS)
- Mini-Mental state Examination (MMSE)

Healthcare utilization resources and patient's beliefs on medication will be measured using the following tools:

- HCRU (Healthcare resource utilization questionnaire)
- Beliefs Medication questionnaire (BMQ)

Safety Variables:

The physician will be asked to report Serious Adverse Events (SAEs), Product Complaints (PCs), and pregnancies.

Data Sources: Source documents are defined as original documents, data and records. These may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and/or x-radiographs. Data collected during this PMOS must be recorded on the appropriate source documents. The only exception will be for patient/caregiver-completed questionnaires. There will be no corresponding source documentation for the latter, because the patient/caregiver completes the forms directly on the paper questionnaire (that is, these questionnaires are the source data). Patient/caregiver self-administered questionnaires will be completed on paper forms and then submitted to the designated CRO for data entry into the eCRF system.

The PMOS physician/institution will permit PMOS-related monitoring, audits, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review, and regulatory inspection(s), providing direct access to source documents.

Study Size: The sample size of approximately 400 patients has been determined based on the rationale of the study.

Sample size calculation was based on pre-defined precision of the estimators of the primary endpoints, expressed as the maximum length of the corresponding two-sided 95% confidence intervals. In order to achieve a precision of ± 5% (i.e. the confidence intervals are not wider than 10%), at least 385 (evaluable) patients are necessary.

In this observational retrospective and cross-sectional study, only a small number of non-evaluable patients are expected. Therefore, it is planned to include a total number of approximately 400 patients.

Data Analysis:

All data assessed will be analyzed using descriptive statistics. All statistical analyses will be carried out by means of the SAS® package (version 9.4 or higher).

Two-sided 95% confidence intervals will be provided for primary and secondary endpoints defined by proportions. Confidence intervals will also be calculated for differences between pre-defined groups of patients, if appropriate (e.g. LCIG monotherapy vs. LCIG plus add-on PD medication).

Logistic regression and subgroup analyses will be applied to investigate the impact of potential prognostic factors on the primary endpoints and to identify predictors for LCIG monotherapy.

Milestones: Enrollment will be completed within approximately 12 months.

Planned start date (FPI) 15th Dec 2017

Planned end date (LPO) 15th Dec 2018

Final Report of Study Results (CSR) 15th November 2019

5.0 Amendments and Updates

Not applicable

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection (FPI):	15th December 2017
End of Data Collection (LPO):	15th December 2018
Study Progress Report X:	Not applicable
Interim Report X:	Not applicable
Registration in the EU PAS register	Not applicable
Final Report of Study Results:	15th November 2019

7.0 Rationale and Background

Parkinson's disease (PD)

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder with a worldwide estimated prevalence of 0.3% in the general population 40 years of age and older [1]. As incidence and prevalence rise with age, more than 1% of the population over the age of 65 is afflicted with PD [12-14]. The mortality for elderly PD patients is two to five times higher than in age-matched controls [15]. PD is caused by idiopathic degeneration of dopamine-producing cells in the *substantia nigra* of the midbrain [16]. The resulting dopamine depletion disrupts connections to the motor cortex and the thalamus, leading to the clinical cardinal signs of PD: resting tremor, cogwheel rigidity and bradykinesia, along with postural instability [17]. Additional diagnostic criteria are asymmetrical onset of symptoms and symptomatic response to levodopa (LD) [17, 18]. Due to PD's distinctive clinical signs and for the lack of confirming diagnostic tests, diagnosis is generally based on the clinical picture and supported by the observation of a clinical improvement upon dopaminergic drug therapy [19-21].

The most effective symptomatic therapy for PD remains levodopa (LD), a precursor of dopamine. LD is usually administered together with carbidopa, a decarboxylase-inhibitor that improves the bioavailability of levodopa in the central nervous system. However, within several years of levodopa therapy initiation, a considerable number of patients develop complications, and after 5 to 10 years of treatment at least 50% of patients develop motor fluctuations and abnormal involuntary movements (dyskinesia) [22]. Possible causes for those detrimental LD effects include the sensitization of postsynaptic receptors after oral, pulsatile stimulation, and also the progressive degeneration of the nigrostriatal dopamine terminals that take up exogenously administered LD and convert it to dopamine for subsequent storage and release [2, 22-24]. In consequence, patients in the advanced stages of the disease experience an enhanced sensitivity to small changes in plasma LD levels, which narrows the therapeutic window and negatively impacts motor function [25, 26]. As there is no gastric absorption of LD, gastric emptying and transit via the pyloric sphincter are critical factors for regular intestinal LD absorption [27]. Gastrointestinal dysfunction with erratic gastric emptying, a symptom many patients develop over the years, impairs intestinal absorption and is another common cause of poor effectiveness of LD in PD.

Motor fluctuations with alternating periods of good and poor symptom control and dyskinesias are a common sign for the progression to the advanced disease stages. In patients with advanced PD (APD), treatment regimens have become complex over the years. Upon the occurrence of complications, initial treatment strategies are based on optimization of oral LD therapy, and may include minimizing oral doses and shortening the dosing intervals. Besides LD, a variety of PD drugs (including dopamine agonists, monoamine oxidase [MAO] B inhibitors, anticholinergic agents, amantadine, catechol-o-methyl transferase [COMT] inhibitors) are available for symptomatic treatment, which may be employed as monotherapy or in combination. However, complex oral drug regimens are particularly burdensome to APD patients, as patients are exposed to

increased risks related to swallowing problems and choking (due to dysphagia), and drug-drug interactions. Moreover, patient adherence to complex oral treatment regimens is often strongly impaired due to progressive cognitive deficits.

As progressive deterioration of the nigrostriatal dopaminergic transmission occurs, even complex oral drug regimens may become insufficient for symptom control [2]. Therefore, other therapeutic strategies have been developed, including treatments based on continuous drug delivery (CDD) [3-5], such as continuous subcutaneous apomorphine infusion therapy (CSAI), or levodopa-carbidopa intestinal gel (LCIG), or even surgical interventions such as implantation of deep brain stimulation (DBS) devices. However, in treatment options such as CSAI and DBS, continued use of PD medication appears to remain necessary for many APD patients. In many cases, CSAI does allow for withdrawal or tapering of other PD treatments such as COMT-inhibitors, dopamine agonists, and MAO-B inhibitors, as well as reductions of levodopa dosages. Still, CSAI is only rarely used as monotherapy as this is often limited by poor tolerability of high doses of apomorphine [28-32]. Studies on DBS treatment show that, even though DBS may enable reductions in the dosing of PD medication by 35-60%, patients can very rarely be managed without any additional therapy [28, 33, 34].

Levodopa-Carbidopa Intestinal Gel (LCIG)

Various levodopa CDD formulations (intravenous and enteral) have been under investigation for already more than 30 years [35-37]. Among the enteric CDD formulations, levodopa-carbidopa intestinal gel (LCIG) is the only formulation of LD and carbidopa which has been found to be suitable for continuous long-term intestinal infusion so far [38]. The LCIG system has been on the market for over 10 years, and is currently approved in more than 40 countries in the treatment of levodopa-responsive APD. In the

majority of countries, it is marketed by AbbVie (AbbVie Ltd, United Kingdom) under the trade names Duodopa® and Duopa® (in the United States).

The LCIG suspension is provided in 100 mL cassettes to be connected to an ambulatory pump (CADD-Legacy® 1400 portable pump) that delivers the cassette content directly into the duodenum. The LCIG infusion rate is programmable and can be adjusted in steps of 0.1 mL/h (equivalent to 2 mg levodopa/h). In addition, patients can self-administer extra doses during the day by pressing a dose button to infuse a pre-programmed bolus (usually 10 to 20 mg per bolus). Patients may also (if instructed to do so by their treating physician) adjust the amount of the extra dose according to their needs.

During an optional test phase with application of LCIG via a nasojejunal (NJ) tube, the treatment response and tolerability of LCIG may be assessed before proceeding to the surgical procedure to permanently place a tube into the small bowel. The percutaneous endoscopic gastrostomy with a jejunum tube placement (PEG-J) is a common procedure and typically does not require general anesthesia (mostly conscious sedation) [39]. Although the percutaneous endoscopic gastrostomy (PEG) procedure is relatively safe and major complications are rare, device- and procedure-related undesirable effects may occur. Drug-related undesirable effects that occur frequently with the Duodopa system include nausea and dyskinesia. Device- and procedure related undesirable effects include abdominal pain, complications of device insertion, excessive granulation tissue, incision site erythema, postoperative wound infection, post procedural discharge, procedural pain and procedural site reaction. Less common complications of the PEG procedure observed with the LCIG system include bezoar, ileus, implant site erosion/ulcer, intestinal hemorrhage, intestinal ischemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumoperitoneum and post-operative wound infection [40]. These complications may result in serious events which might impose a need for further surgery, or may be even fatal.

LCIG Clinical Data

LCIG efficacy and safety in patients has been corroborated in many clinical trials in patients with APD [4, 41-44]. Outcomes from a randomized, double-blind, controlled, multi-country study over 12 weeks in 71 patients comparing LCIG and oral levodopa/carbidopa as adjunct therapy to optimized oral treatment have been published [7]. In LCIG patients, a significant reduction in off- time versus baseline and versus oral levodopa/carbidopa as well as an increase in on-time without dyskinesias versus oral levodopa/carbidopa were observed.

A subsequent open-label extension study showed sustained efficacy in patients continuing LCIG therapy [45]. The LCIG-naïve patients, i.e. those previously randomized to oral levodopa/carbidopa in the double-blind phase, showed a similar efficacy with regard to off- and on-time without dyskinesias as the patients randomized to LCIG.

A multi-national study focusing primarily on tolerability and safety enrolled 354 patients with APD who were observed over 54 weeks in an open-label design including a nasojejunal test phase [8, 46]. In this study, 76.8% of patients completed the study, while 7.6% of patients withdrew due to AEs. The efficacy findings confirmed the data of the above described double-dummy study [7] showing similar reductions in daily off-time and increases in on-time without dyskinesias over 1 year, and also showed sustained effects under stable levodopa doses.

In addition, interim data from an ongoing post-marketing observational study on the use of LCIG in routine care conditions showed sustained improvements in off-time and on-time with dyskinesias, as well as improvements in Unified Parkinson's Disease Rating Scale (UPDRS) II and III scores during on-time. According to the 12-month interim outcomes of the first 172 included patients, the mean LCIG dose remained stable and the

tolerability and safety data were consistent with the established safety profile of LCIG [10].

LCIG and add-on PD medication use

According to the label outside of the United States, LCIG should be initially used as a monotherapy [40]. In clinical practice however, a transitory titration period is usually needed during which all other oral or transdermal therapies are tapered. Many patients are expected to be treated sufficiently by LCIG daytime infusions. Some patients, however, may need additional therapy for the night time and eventually add-on combination therapy may be warranted, in order to increase bioavailability and effectiveness [47].

Data from the above mentioned clinical trials [7, 8, 46] also suggest that LCIG treatment can reduce the need for other PD medication.

In the pivotal clinical trial on LCIG [7], patients had to be receiving stable doses of oral levodopa for at least four weeks prior to enrollment. If receiving sustained release levodopa-carbidopa, levodopa-carbidopa-entacapone or other formulations of levodopa, they had to be converted to equivalent doses of levodopa-carbidopa immediate release (LC-IR) formulations and remain on stable doses for at least four weeks before enrollment. During the double-blind phase patients had to stay then on their prior PD medication (to ensure blinding). Upon entering the open-label extension study, when adjustment of concomitant PD medication was again permitted, these were discontinued in many patients on LCIG. A subanalysis showed that percentage of patients on add-on PD medication dropped from 89% (n = 71) during the double-blind to 37% (n = 62) by day 1 of the extension study [6].

In the second, open-label clinical trial, 80% of patients were on add-on PD medications upon study start. As per study protocol, prior to LCIG initiation, tapering of add-on PD

medication was required and limited to oral LD medication, after 4 first weeks of the study, the add-on PD medication could be reintroduce. By end of the study (week 54), 77% of patients remains on LCIG monotherapy [6, 8].

Importantly, those two clinical trials differed, among other aspects, in the required tapering process: in one study, tapering was required prior to LCIG initiation [8, 46], while in the other study, tapering was optional and the timing prior to or after LCIG initiation was not specified [7]. Comparing the results of both studies, the method of tapering did not appear to have a clear impact on adverse events, specifically, no differing rates of dyskinesia or signs of dopamine withdrawal were observed [6]. In both clinical trials, certain add-on PD medications, including other levodopa preparations or apomorphine sub-cutaneous (SC), were not allowed, and data are thus not easily translatable to real-world practice.

In a multinational registry on the efficacy and safety of LCIG in routine care (GLORIA registry), 36-40% of APD patients were treated over 24 months with LCIG monotherapy (without any additional oral PD medication); however no background information on the rationale for the use of add-on medication (e.g., introduction/tapering/maintenance) was collected [11].

Interim outcomes of the GREENFIELD observational study on 145 patients with APD in Italy compared clinical data before and during LCIG therapy. Initiation of LCIG led to significant clinical improvement and the intake of add-on PD medication was largely reduced: for instance, oral levodopa use decreased from 96.9% before LCIG start to 5% (during the day) and 26% (at night); use of dopamine agonists decreased from 64.1% to 30%. However, thus far, results are only derived from a mean treatment period of 14 months, and date are still incomplete [9].

Rationale

LCIG (Duodopa®) appears to possess the potential to be used as monotherapy in many patients, or at least enable significant reductions of the add-on PD medication. Thereby, LCIG may achieve a much-needed simplification of the treatment regimen, allowing for a reduction of detrimental drug-drug interactions [6].

So far, data on patients in whom LCIG monotherapy or significant reductions of add-on PD medication was achieved, have been derived from two clinical studies with rigorous protocols [7, 8], and therefore cannot be easily translated into routine clinical practice. Also, recent observational studies demonstrated overall varying approaches in the management of add-on PD medications in routine clinical practice before and after initiation of LCIG treatment [9, 10].

For APD patients under LCIG treatment there is an opportunity to substantially reduce the need for other add-on PD medication and/or completely discontinue them. This is the primary hypothesis that generates this study.

In summary, no systematic, comprehensive and homogeneous real-world data are available – neither on LCIG monotherapy or LCIG in combination with add-on PD medication, nor on the management (reasons for use and time course) of add-on PD medications before or upon LCIG initiation, or during long-term LCIG maintenance therapy.

The present study attempts to fill this knowledge gap and generate relevant data from routine clinical practice on the usability of LCIG as a monotherapy and in combination with add-on PD medications. In addition, useful data on the handling of add-on PD medication (e.g., tapering, introduction), upon LCIG initiation and over long-term use shall be collected.

8.0 Research Question and Objectives

The primary objective of this multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) is to evaluate the percentages of Advanced PD patients on LCIG monotherapy right after LCIG initiation and at 3, 6, 9, and 12 months, respectively.

The secondary objectives are:

- To describe PD medication management, and the main reasons justifying their use, directly prior to LCIG initiation, at LCIG initiation and during long-term LCIG treatment
- To describe LCIG infusion settings and substantial dose adjustments and the respective reasons
- To describe the Healthcare Resource Utilization (HCRU)
- To identify the physician's and patient's/caregiver's overall preference for the pharmacological treatment approach using LCIG as monotherapy vs. LCIG plus add-on PD medication
- To identify predictors for achieving long-term monotherapy with LCIG vs. LCIG plus add-on PD medication, based on the patient's profile and the physician's profile
- To describe the latency from LCIG initiation until LCIG is given as a monotherapy and the average duration of LCIG monotherapy

- To describe the latency from the initiation of LCIG therapy until the introduction or tapering of each PD medication, or until substantial dose adjustments of LCIG
- To evaluate the percentage of patients who are on LCIG monotherapy, PD medication management and HCRU for the participating countries who have enrolled a minimum of 20 study subjects.

9.0 Research Methods

9.1 Study Design

This is a multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) of patients with APD treated with LCIG in a routine clinical setting. Patients who are receiving LCIG according to the approved local product label and reimbursement guidelines will be asked to participate.

This study will include a retrospective section, collecting below specified data from patient's medical records from the time of the decision to start LCIG treatment until the present day, and a single study visit (cross-sectional) with clinical status and subjective assessments of patients at present time.

Patients, who have received LCIG for at least 12 months, and who satisfy all the inclusion criteria and none of the exclusion criteria will be eligible to be enrolled into this PMOS. All eligible LCIG patients will be identified consecutively and offered the opportunity to participate in the study.

To assess the generalizability of the data from the patients enrolled, the physician will be asked to document on a separate Case Reporting Form the number of patients who are eligible but refuse to participate in the study. Only age ranges (<30 years, 30-45 years, 45-65 and > 65 years) and reason(s) for not participating will be collected.

The primary endpoint of this PMOS will be the percentages of APD patients on LCIG monotherapy right after LCIG initiation and at 3, 6, 9, and 12, respectively.

The secondary endpoints are:

- Descriptive data from patient's PD medication:
    - For add-on PD medication: percentage of patient on each PD medication (by drugs and class), total daily dose and levodopa equivalent Daily dose (LEDD) , posology (number of times per day);
    - For LCIG infusion settings and substantial dose adjustments: total dose per day and specific for each type of dose (morning dose and continuous dose) and number of hours of infusion.

- Tapering process: number of days required for the tapering process, total dose per day and posology for add-on PD medication prior to LCIG initiation, at LCIG initiation (titration) or during ongoing LCIG treatment
- Main reasons for introduction or tapering of add-on PD medication or LCIG substantial dose adjustments

- Latency and duration of treatments data:
  - Number of days or months from LCIG initiation until LCIG is given as a monotherapy and the duration of LCIG monotherapy.
  - Number of days or months from LCIG initiation until the introduction or tapering of each PD medication, or until any LCIG substantial dose adjustments.
- LCIG monotherapy vs LCIG plus add-on PD medication data:
  - Healthcare Resource Utilization, as measured by Healthcare Resource Utilization Questionnaire (HCRU)
  - Patient's, caregiver's, and physician's overall preference on LCIG monotherapy vs. LCIG plus add-on PD medication, percentage of patient's and physician's preference for each of the options
  - Predictors for LCIG as monotherapy vs. LCIG plus add-on PD medication based on the patient's profile, including socio-demographics, clinical status (motor and non-motor symptoms), Levodopa-equivalent dose (LED), PD medication and Quality of Life
  - Predictors for LCIG as monotherapy vs. LCIG plus add-on PD medications based on the physician's profile including experience as measured by number of years on APD patient management, number of years using LCIG therapy, and number of patients on LCIG therapy

9.2 Setting

9.2.1 Number of patients to be enrolled

Approximately 400 adult patients diagnosed with APD, on current treatment with LCIG, and treated with LCIG for at least 12 months prior to study inclusion, will be enrolled in approximately 15 countries in Europe (Austria, Bulgaria, Croatia, Romania, Czech Republic, Estonia, Hungary, Ireland, Germany, Netherlands, Slovakia and Spain), Canada and Australia, among others, the final list of participating countries to be confirmed. All eligible patients at a given site will be enrolled consecutively in order to minimize selection bias.

9.2.2 Site Selection Criteria

The participating sites will be hospitals or clinics experienced in treating patients with APD, and with experience in LCIG treatment. Sites must have the ability to appropriately conduct the PMOS in accordance with applicable legal and regulatory requirements. Participating physicians should have been involved in the respective patient's management since initiation of LCIG therapy.

9.2.3 PMOS Duration

This PMOS consists of one single visit. The observational period is mainly retrospective and includes one cross-sectional study visit. Data gathered are derived from the time prior to initiation of LCIG therapy until the day of the study visit (see Figure 1).

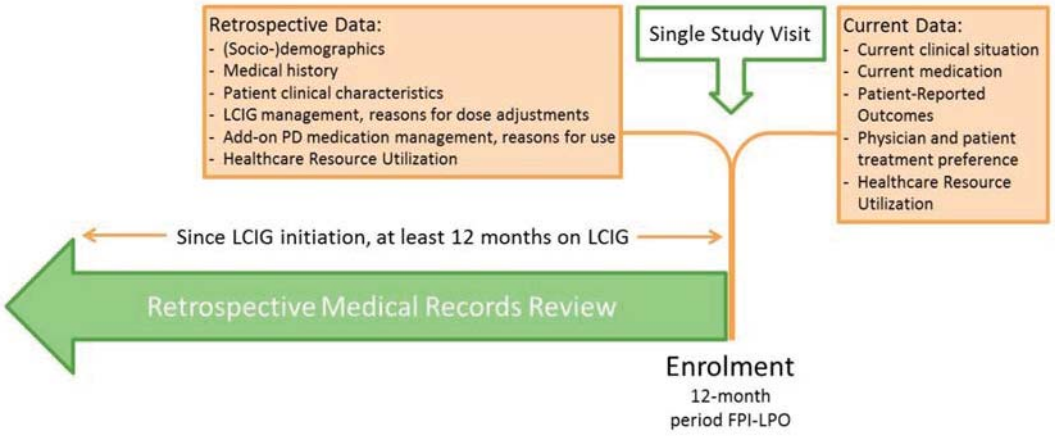

Figure 1: Study Schematic

9.2.4 Inclusion Criteria

1. Patients diagnosed with APD and on LCIG treatment for at least 12 months
2. Patient must have been on continuous LCIG treatment for at least 80% of days in the preceding year
3. Patients must be treated by the same physician (PI or co-investigator) since the initiation of LCIG treatment
4. Decision to treat with LCIG was made and therapy was started by the physician prior to any decision to approach the patient to participate in this study
5. Prior to any data collection, the patient, or legal authorized representative (LAR) has voluntarily signed an Authorization for Use/Disclosure of Data (AUDD)/informed consent form (ICF) according to national regulations after the study has been explained and the subject has had the opportunity to have questions answered

9.2.5 Exclusion Criteria

1. Participation in a concurrent or a previous interventional clinical trial during which the patient was on LCIG therapy
2. Lack of motivation or insufficient language skills to complete the study questionnaires

9.2.6 PMOS conduct

Physicians will be provided with study information including a protocol, AUDD/ICF template, paper-based patient questionnaires, and access to the electronic Case Report Forms (eCRFs).

The study visit will take place during a regular clinic visit as foreseen per routine clinical practice.

Clinical data associated with this PMOS will be collected electronically (eCRF) via a web based electronic data capture (EDC) system. Access to the EDC system is granted by logging in with username and password. Patient/caregiver self-administered questionnaires will be completed on paper forms and then entered into the database by the designated contract research organization (CRO) GKM Gesellschaft für Therapieforschung mbH, Munich, Germany.

9.2.7 PMOS Procedures

Data for this PMOS will be collected during one single patient visit in accordance with routine clinical practice as indicated in Table 1, Summary of Assessments.

9.2.7.1 Center characterization

The physician will provide information on the site, including institution type, origin of service, average number of PD and APD patients seen at site per year, number of physicians managing PD patients at site, support services/functions available at the site, access to device aid therapies treatments, and average yearly frequency of visits of PD and APD patients (on device-aided therapy).

9.2.7.2 Physician's profile

The physician is requested to document his/her experience in the treatment of APD patients and in the use of LCIG, including therapeutic specialty/-ies, number of years within the management of PD and APD patients, number of years working at current institution, observance of standard treatment algorithm/established guidelines, overall preference on LCIG as monotherapy vs. LCIG plus add-on PD medication, and years of experience and number of patients with LCIG, DBS or CSAI.

9.2.7.3 Patient Demographics and socio-demographics

The physician will collect patient demographic information and record it on the eCRF. The demographic information includes age, sex, race and ethnicity, and education (where applicable and allowed).

Socio-demographic data to be collected before LCIG initiation and at the patient visit and includes information on living situation, current primary occupation, and the need of a caregiver (and extent of care needed)

9.2.7.4 Medical History and PD History

A complete medical history (PD and non-PD) will be obtained and recorded in the eCRF as available from the patient files. Information on PD includes phenotype, date of first PD

diagnosis, year of first occurrence of motor fluctuations, percentage and daily hours spent in off state or spent in on-state with troublesome/non-troublesome dyskinesia, presence of PD symptoms (motor and non-motor), Unified Parkinson's Disease Rating Scale (UPDRS), Modified Hoehn & Yahr stage (UPDRS part V), and PD-related comorbidities.

9.2.7.5 Previous PD medication and add-on PD treatment during LCIG Treatment

Data on previous PD medication (right before initiation of LCIG treatment) will include date of drug initiation and/discontinuation, reason for its discontinuation, drug name, total dose per day, posology, and attempts of previous device-aided therapies (e.g., CSAI, DBS).

Data on add-on PD medication upon LCIG initiation or during LCIG treatment will include date of drug initiation/discontinuation, drug name, total dose per day, posology, tapering* process (duration and posology), starting and end date of LCIG titration, reasons for add-on drug therapy (severity and frequency), timing of add-on drug (during/outside of infusion hours).

Levodopa equivalent daily dose (LEDD) table published by Tomlinson, et al will be used to calculate LEDD. [47]. Each PD medication amount should be multiplied by the appropriate value to obtain the corresponding LEDD. Adding together the corresponding LEDD for each PD medication, will be providing the total LEDD.

*The term "tapering" is used within this study in the context of drug treatment. It refers to the process of reducing a certain drug dosage incrementally (over a few days or weeks), instead of its abrupt discontinuation. For some PD medications a tapering process is needed to avoid a withdrawal syndrome

9.2.7.6 Concomitant Disease and Medication

Information on concomitant disease and medication (non-PD treatment) will be collected and reported in the eCRF, including drug name, indication, start/stop date, and dosages.

9.2.7.7 LCIG Treatment

Information on LCIG treatment from initiation until the day of the visit will be documented in the eCRF, including reason(s) for initiation of LCIG treatment, date of introduction of LCIG, use of nasojejunal tube, date of PEG-J procedure, date of titration and duration of titration process, infusion settings (infusion time, morning dose, continuous infusion rate, total daily dose) and dose modification (number of dosage changes, new infusion settings or temporary interruptions in LCIG daily infusion rate and reasons for dosage adjustment).

A LCIG substantial dose adjustment is defined as any increase or decrease of the total daily LCIG dose by more than 20% of total daily dose.

LCIG monotherapy is defined as being treated with LCIG as the only PD medication that the patient is taking during the LCIG infusion hours. LCIG long term monotherapy is defined as a time period of at least 12 months of continuous LCIG monotherapy.

9.2.7.8 Current APD Status at study visit

- Parkinson's disease status will be measured by the physician using the following scales: mentation/behaviour/mood (UPDRS I), activities of daily living (UPDRS II), motor examination (UPDRS III), complications of therapy (UPDRS IV) and Modified Hoehn and Yahr Stage (UPDRS V),non-motor symptoms (NMSS) will be recorded and Mini-Mental State Examination (MMSE).

  The patient will be requested to fill in the following questionnaires:

  - Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease- Rating Scale (QUIP-RS)
  - Parkinson's disease Sleep Scale Version 2 (PDSS-2).

9.2.7.9 Healthcare Resource Utilization

The HCRU Questionnaire will contain questions on the occupational status, nursing home visits, hospitalizations, emergency care visits, caregiver support, including the patient's opinion on PD medication as retrieved by the following questionnaires, which the patient will be requested to complete:

- Beliefs Medication Questionnaire (BMQ)

In addition, the patient/caregiver will be requested to state their overall preference on LCIG as a monotherapy vs. LCIG plus add-on PD medication.

9.2.7.10 Quality of Life

In order to assess the patient's quality of life, the patient will be asked to complete the Parkinson's disease Quality of Life Questionnaire (PDQ-8).

Table 1 Summary of assessments

Observation	Before LCIG initiation	LCIG initiation	During LCIG treatment	Patient visit
	Retrospective Data from Patient Files			
Center Characterization	X			
Physician experience and treatment preference	X			
Patient demographics	X			
Patient socio-demographics	X			X
Medical History and PD History	X			X
PD medication before starting LCIG	X			
Reason(s) for LCIG initiation		X		
LCIG infusion data		X	X	X
Add-on PD medication since LCIG initiation		X	X	X
Concomitant Medication (non-PD treatment)	X	X		X
Behaviour/mentation/mood (UPDRS Part I)				X
Activities of daily living (UPDRS Part II)				X
Motor examination (UPDRS Part III)				X
Treatment complications (UPDRS Part IV)				X
Disease Stage (ModifiedHoehn & Yahr stage, UPDRS Part V)	X			X
Non-motor Symptoms Scale (NMSS)				X
Questionnaire for Impulsive-Compulsive Rating Scale (QUIP-RS)				X
Mini-Mental State Examination (MMSE)	X			X
Quality of Life (PDQ-8)				X
Parkinson's disease Sleep Scale Version 2 (PDSS-2)				X
Healthcare Resource Utilization Questions	X			X
Beliefs Medication				X

Questionnaire (BMQ)				
Adverse events, pregnancies				x
Product complaints				x

9.3 Variables

9.3.1 Safety Variables

The physician will be asked to document all AEs, product complaints and pregnancies on eCRFs (Section 11.1 and 11.2)

SAEs (Section 11.1) and product complaints (PCs, Section 11.2) as defined and pregnancies that have occurred from the time the physician obtains the patient's authorization to use and disclose information must be reported to AbbVie within 24 hours of the study visit.

In addition, any prior suspected adverse reactions (adverse events considered to be likely related to an AbbVie product) identified in the patient's file should be reported (Section 11.1.5.1).

9.3.2 Clinical variables

Information about the previous PD medication, and add-on PD medication and LCIG infusion settings will be retrospectively collected from patient`s medical records.

Actual Parkinson's disease status and motor symptoms/motor complications will be measured using the following tools:

- Duration of OFF time and dyskinesia (hours during the day prior to the clinical visit) as reported by the patient
- UPDRS Parts III (motor evaluation) and IV (Treatment complication)

The following health outcomes will be measured using the following tools:

- UPDRS Part I (evaluation of mentation, behavior, and mood)
- UPDRS Part II (self-evaluation of the activities of daily living (ADLs))

- UPDRS Part V (Modified Hoehn and Yahr stage of severity of Parkinson's disease)
- PDQ-8 (Parkinson´s Disease Questionnaire) to evaluate PD patient's quality of life.

The following Non-motor symptoms including sleep/daytime sleepiness, impulse control disorders and mental status will be measured using the following tools:

- Non-motor Symptoms Scale (NMSS)
- Parkinson´s Disease Sleep Scale-2 (PDSS-2)
- Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale (QUIP-RS)
- Mini-Mental State Examination (MMSE)

The following healthcare utilization resources and patient's beliefs on medication will be measured using the following tools:

- HCRU (Healthcare resource utilization questionnaire)
- Beliefs Medication questionnaire (BMQ)

9.4 Data Sources

9.4.1 Source documents

Source documents are defined as original documents, data and records. These may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and/or x-radiographs. Data collected during this PMOS must be recorded on the appropriate source documents. The only exception will be for patient/caregiver-completed questionnaires. (i.e. PDSS-2, PDQ-8, QUIP-RS). There will be no corresponding source documentation for the latter, because the patient/caregiver completes the forms directly on the paper questionnaire (that is, these questionnaires are the source data). Patient/caregiver self-administered questionnaires will be completed on paper forms, double-checked for completeness by the site personal

participating in the study and then submitted to the designated CRO GKM for data entry into the eCRF system.

The PMOS physician/institution will permit PMOS-related monitoring, audits, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review, and regulatory inspection(s), providing direct access to source documents.

9.4.2 Product supply

Since this is a PMOS, the patient will be treated in accordance with the physician's usual and customary medical practice. AbbVie will not provide any medication or therapy for this PMOS.

9.4.3 Health Outcomes

9.4.3.1 Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) [49] is an Investigator-used tool to follow the longitudinal course of Parkinson's disease. The UPDRS assessment will be performed by an experienced rater. Rater training will be provided by the Sponsor as appropriate.

The UPDRS is includes of the following sections:

- Part I – Mentation, Behaviour, and Mood; total score range 0-16
- Part II – Activities of Daily Living (ADL); total score range 0-52
- Part III – Motor Examination; total score range 0-108
- Part IV – Complications of Therapy; total score range 0-23
    - Dyskinesias and Dystonia (Part IV, items 32-35); total score 0-13
    - Motor fluctuations (Part IV, items 36-39); total score range 0-7
    - Other complications (Part IV, items 40-42); total score range 0-3
- Part V – Modified Hoehn & Yahr Stage

The dimensions are evaluated through a physical examination and interview carried out by the neurologist. The patient score can be between 0 and 199, where 199 points indicates complete disability. In this PMOS, all five sections of the UPDRS will be used.

9.4.3.2 Non-Motor Symptoms Scale (NMSS)

The NMSS is a comprehensive investigator-completed validated tool measuring a broad range of non-motor symptoms in PD patients. The scale is aimed to be practical and quantitative, encompassing the whole range of non-motor symptoms experienced by people with PD. The NMSS measures the frequency and severity of these symptoms and comprises 30 questions covering 9 domains of patient symptom experience (cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, GI tract, urinary, sexual function, and miscellaneous [pain, taste/smell, weight change, excessive sweating]) [50, 51]. The NMSS measures the burden of non-motor symptoms by weighting each symptom by its frequency and severity; thereby, providing a quantitative measure that captures infrequent but severe symptoms (e.g., hallucinations) and less serious but frequent symptoms (e.g., fatigue, constipation) and provides the overall global burden for patients. Scores are calculated for each domain as well as a total score. Severity and frequency are rated using a 4-point scale ranging from 0 (none) to 3 (severe; major source of distress or disturbance to subject) for severity and from 1 (rarely) to 4 (very frequent [daily or all the time]) for frequency. The total NMSS score ranges from 0 to 360.

9.4.3.3 Parkinson's Disease Questionnaire (PDQ-8)

The PDQ-8 [52] is a disease-specific instrument designed to measure aspects of quality of life that are relevant to subjects with PD, and which may not be included in general health status questionnaires. The PDQ-8 is a self-administered questionnaire and is a patient reported outcome measure. Each item is scored on the following 5-point scale: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Often, 4 = Always (or "cannot do at all", if applicable).

Higher scores are consistently associated with the more severe symptoms of the disease such as tremors and stiffness. The results are presented as eight discrete domain scores and as a summary index. The PDQ-8 domain scores and summary index range from 0 to 100, where lower scores indicate a better perceived health status.

9.4.3.4 Parkinson's Disease Sleep Scale-2 (PDSS-2)

Although a number of scales exist in evaluating sleep disturbance, only 3 are endorsed and recommended by the Movement Disorders Society [53]. One such scale specific for Parkinson's disease is the Parkinson's Disease Sleep Scale (PDSS), and its modified version, the PDSS-2. The purpose of the PDSS-2 scale is to characterize the various aspects of nocturnal sleep problems in PD patients. The PDSS-2 instrument has been shown to be reliable, valid, precise, and a potentially treatment responsive tool for measuring nocturnal disabilities and sleep disorders in PD [54]. PDSS-2 consists of 15 questions evaluating motor and non-motor symptoms at night and upon wakening, as well as disturbed sleep grouped into 3 domains: motor symptoms at night (5 items), PD symptoms at night (5 items), and disturbed sleep (5 items). Specifically, questions assess overall sleep quality, insomnia, sleep fragmentation, Restless Legs Syndrome (RLS) and periodic limb movements of sleep (PLMS), REM (rapid eye movement) sleep behaviour disorder (RBD), hallucinations, nocturia, nocturnal immobility, pain and cramps, morning akinesia, cramps and tremor, and sleep apnea. The PDSS-2 was developed from the PDSS based upon the need for a treatment/measuring tool containing PD-specific sleep disorders. The instrument was extended to address specific sleep disturbances such as RLS, akinesia, pain, and sleep apnea. Daytime sleepiness was removed from the PDSS-2, as it is a more complex PD symptom. To increase ease of use, the visual analogue scale of the PDSS was transformed into a frequency measure in the PDSS-2. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). Scores are calculated for each domain as well as a total score. The recall period is for the previous week before the study visit.

9.4.3.5 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease- Rating Scale (QUIP-RS)

The QUIP-RS is a fairly novel self-administered rating scale for the evaluation of the symptoms of impulsive compulsive disorders (ICD). ICD may occur in PD patients under dopaminergic drug therapy, also called dopaminergic dysregulation syndrome [55, 56]. QUIP-RS has been shown to have very good sensitivities and appears to be a valid instrument in the evaluation of ICD in patients with APD [57].

The QUIP-RS is completed by the patient. The QUIP-RS uses a 5-point Likert scale upon which each symptoms is rated based on frequency (i.e. [0] = not at all, [1] = rarely, etc.). There are four primary questions, related to the 4 ICDs (compulsive gambling, buying, eating, and sexual behaviour), and 3 related disorders (medication use, punding, and hobbyism). The total QUIP-RS score ranges from 0 to 112 [57].

9.4.3.6 Healthcare Resource Utilization (HCRU)

The HCRU questionnaire will contain questions on the occupational status, nursing home visits, hospitalizations/emergency care visits and reason, caregiver support, patient´s opinion on PD medication (Belief Medication questionnaire -BMQ-)) and other items with respect to healthcare resource utilization.

- The Beliefs Medication Questionnaire (18-items BMQ) is a tool for screening patients' beliefs, attitudes and concerns regarding their medication. It consists of a general section, which assesses general beliefs about medicines, and a specific section which comprises factors assessing beliefs about necessity and concerns about the currently prescribed medications [58].

9.4.3.7 Mini-Mental State Examination (MMSE)

The MMSE [59] is a brief, 30-point questionnaire, administered by a trained rater, which provides a quantitative measure of cognitive mental status in adults and is widely used to screen for cognitive impairment and to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in a patient over time, and

to document response to treatment. In this study, MMSE will be used to evaluate cognition status at cross-sectional visit, and if available to collect it before starting LCIG treatment.

9.5 Study Size

The primary objective of this PMOS is to estimate the percentages of APD patients on LCIG monotherapy right after LCIG initiation and at 3, 6, 9, and 12 months, respectively.

Sample size calculation was based on pre-defined precision of the estimators, expressed as the maximum length of the corresponding two-sided 95% confidence intervals. In order to achieve a precision of ± 5% (i.e. the confidence intervals are not wider than 10%), and considering an underlying percentage of 50% (i.e. the percentage which leads to the largest sample size), at least 385 (evaluable) patients are necessary.

In this PMOS, only a small number of non-evaluable patients are expected. Therefore, it is planned to include a total number of approximately 400 patients.

9.6 Data Management

CRFs must be completed for each patient enrolled in this PMOS. These forms will be used to transmit information collected during the PMOS to AbbVie and regulatory authorities, as applicable. The CRF data for this PMOS are being collected with an electronic data capture (EDC) system, Rave®, provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the PMOS-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the PMOS-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie. The investigator will document patient data in his/her own patient files. Questionnaires filled in by the patients will be source data (e.g., QUIP-RS, PDQ-8, PDSS-2, BMQ). All eCRF data required by this protocol will be recorded in the EDC system. All data entered into the eCRF will be supported by source documentation, except for questionnaires that are completed by the physicians

(UPDRS, NMSS). Only the investigator or an authorized member of the investigator's staff will able to change or correct eCRF data. All changed information, including the date and person performing the changes, will be available via the EDC audit trail. For any eCRF correction, a reason for the alteration must be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the PMOS in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof. Access to the web-based EDC system for the duration of the PMOS is protected by an individual account (consisting of username and password). This access will be removed from investigator sites at the end of the site's participation in the PMOS. Data will be subject to automatic and manual plausibility checks and implausible data will be queried by means of queries in the EDC system; in case of technical issues, paper based query forms will be sent to the sites.

Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

9.7 Data Analysis

Summary of data collected from retrospective patient´s medical records and single study visit will be presented using descriptive statistics.

Quantitative data (e.g. age) will be analyzed by the statistical parameters valid N, missing N, mean, standard deviation (SD), and selected quantiles: minimum (0%), lower quartile (25%), median (50%), upper quartile (75%), and maximum (100%). If indicated by the data, an additional frequency distribution will be supplied after appropriate grouping of data.

Qualitative (e.g. gender) and categorical variables (e.g. individual items of questionnaires) will be presented by (absolute and relative) frequency distributions. For categorical variables associated with score values, the mean will be calculated as well.

Two-sided 95% confidence intervals will be provided for primary and secondary endpoints defined by proportions. Confidence intervals will also be calculated for differences between pre-defined groups of patients, if appropriate (e.g. LCIG as monotherapy vs. LCIG plus add-on therapy).

Logistic regression and subgroup analyses will be applied to investigate the impact of potential prognostic factors for LCIG monotherapy. Potential prognostic factors used for the regression model will include demographic variables (ie. age, gender, race) and baseline disease characteristics at LCIG initiation (PD duration, hours of OFF time, hours of dyskinesia, Levodopa equivalent daily dosage).

Details of statistical methods will we presented in a separate statistical analysis plan (SAP). All statistical analyses will be carried out by means of the SAS® package (version 9.4 or higher).

9.8 Quality Control

The personnel at each PMOS site may be trained on the protocol and PMOS procedures by a CRA at a site training visit, via telephone or on-site.

Throughout the PMOS, the CRO and AbbVie will periodically follow-up with sites to ensure that SAEs and PCs are being reported.

All PMOS data will be entered into the eCRF which will be accessed via a web-based EDC system. Any necessary corrections will be made to the database and documented via queries, source data clarification form or audit trail. A manual review of elected line listings will also be performed at the end of the PMOS. A clinical monitor working on behalf of AbbVie will perform a final site closure visit when the site or study is closed.

9.9 Limitations of the Research Methods

The primary limitation of this PMOS is that it is performed in an open-label, non-controlled and non-randomized design with mainly retrospective data capturing. Thus, selection and reporting bias cannot be excluded. In order to minimize these biases, all eligible patients shall be enrolled in a consecutive manner.

Moreover, as only patients on current LCIG therapy are included, data of patients who discontinued treatment will not be collected. Therefore, comprehensive safety conclusions may not be drawn from the study results.

Finally as the study aims to identify treatment predictors based on patient´s and physician´s profiles; however it can be influenced by LCIG country specific prescription or reimbursement status. Therefore, country origin would be taken into account when analyzing treatment predictors.

9.10 Other Aspects

Not applicable

10.0 Protection of Human Subjects

A signed and dated Authorization for Use/Disclosure of Data (AUDD)/informed consent form (ICF) will be obtained from patients or their legal authorized representative (LAR) before the release of any information or participation in the PMOS. Before the patient AUDD/ICF is obtained, the physician or designee will explain to the patient/caregiver (LAR) the nature and purpose of the PMOS and the data to be provided to the Sponsor. An AUDD/ICF template will be provided to the investigator by AbbVie, which can be modified according to local requirements. After the AUDD/ICF is signed, the original form will be placed in the patient's medical record and a signed copy should be given to the patient/caregiver.

Information that refers to the identity of patients will be considered confidential for all purposes. Patient identity may not be revealed or divulged. The physician will maintain a

confidential patient identification code list of all patients enrolled in the PMOS (by name and patient number). This list will be maintained at the site and will not be retrieved by AbbVie.

11.0 Management and Reporting of Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 12). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 12.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

11.1.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

11.1.4 Serious Adverse Event Collection Period

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent)

until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

11.1.5 Serious Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system.

Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event

Clinical Pharmacovigilance
Email to: [redacted]
Fax to: [redacted]

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office: [redacted]
Fax: [redacted]
Email: [redacted]

11.1.5.1 Safety Reporting in the Retrospective section of the study

The retrospective section of the study is based on secondary use of data previously collected from healthcare professionals for other purposes. Any suspected adverse reactions (adverse events considered to be likely related to an AbbVie product) identified during the course of the retrospective review of data should be reported to AbbVie clearly

specifying the suspected adverse reaction was identified during retrospective review of the study. Those events are collected only on the "retrospective data collection events section" of the EDC system.

11.1.6 Pregnancy Reporting

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie via the EDC system within 24 hours of the physician becoming aware of the pregnancy.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

12.0 Product Complaint

12.1.1 Definition

A Product Complaint is any Complaint (see Section 11.0 for the definition) related to the biologic or drug component of the product or to the 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.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

12.1.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Please refer to the contact person identified in **Section 14 (Affiliate Agreement page)** of the protocol. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product and/or device should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

13.0 Plans for Disseminating and Communicating Study Results

At the end of the PMOS, a PMOS report and a publication will be written. The required standard PMOS report template must be followed. This report will contain a description

of the objectives of the PMOS, the methodology of the PMOS and its results and conclusions. The PMOS report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this PMOS will be published by AbbVie or by the participating investigators only after agreement with AbbVie.

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15.0 Affiliate Agreement page

AbbVie

COSMOS – P16-831 - COmedication **S**tudy assessing **M**ono- and c**O**mbination therapy with levodopa-carbidopa inte**S**tinal gel

Country < XXXXXXXX>

Sponsor:
Name of Medical Director:
Address:

Phone:
Fax:

Report safety information to:
Name:
Address:

Phone:
Fax:
Email:

Report product complaints to:
Name:
Address:

Phone:
Fax:
Email:

Requirements for non-interventional studies per local laws and regulations:

Competent Authority approval ☐
Competent Authority notification ☐
Competent Authority involvement not required ☐

Competent Authority, other:
_____

Ethics Committee approval ☐
Ethics Committee notification ☐
Ethics Committee involvement not required ☐

Written Patient Informed Consent required: ☐ No ☐ Yes

<Name here>
Affiliate Medical Director

_____ _____
Signature Date

Annex 15. Patient Questionnaires

A. Parkinson's Disease Quality of Life Questionnaire (PDQ-8)

Due to having Parkinson's disease, how often during the last month have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	Had difficulty getting around in public places?	☐	☐	☐	☐	☐
2.	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
3.	Felt depressed?	☐	☐	☐	☐	☐
4.	Had problems with your close personal relationships?	☐	☐	☐	☐	☐
5.	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
6.	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
7.	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
8.	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***.

Thank you for completing the questionnaire.

B. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

C. Parkinson's Disease Sleep Scale-2 (PDSS-2)

Please rate the severity of the following based on your experiences during the past week (7 days).

Very often: This mean 6 to 7 days a week
Often: This mean 4 to 5 days a week
Sometimes: This mean 2 to 3 days a week
Occasionally: This mean 1 day a week
Never

1. Overall, did you sleep well during the last week?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

2. Did you have difficulty falling asleep at night?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

3. Did you have difficulty staying asleep?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

4. Did you have restlessness of legs or arms at night causing disruption of sleep?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

5. Was your sleep disturbed due to an urge to move your legs or arms?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

6. Did you suffer from distressing dreams at night?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

7. Did you suffer from distressing hallucinations at night (seeing or hearing things that do not exist)?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

8. Did you get up a night to urinate?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

9. Did you feel uncomfortable at night because you were unable to turn around in bed or moved due to immobility?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

10. Did you feel pain in your arms or legs which woke you up while sleeping at night?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

11. Did you have muscle cramps in your arms or legs which woke you up while sleeping at night?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

12. Did you wake early in the morning with painful posturing of arms and legs ?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

13. On waking, did you experience tremor?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

14. Did you feel tired and sleepy after waking in the morning?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

15. Did you wake up at night due to your own snoring or difficulties with breathing?

☐ Very Often ☐ Often ☐ Sometimes ☐ Occasionally ☐ Never

D. Beliefs Medication Questionnaire (18-item BMQ)

Your views about medicines prescribed for you.

- We would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people have made about their medicines.
- Please indicate the extent to which you agree or disagree with them by checking the appropriate box.
- There is no right or wrong answers. We are interested in your personal views.

	Strongly disagree	disagree	uncertain	agree	Strongly agree
1. Doctors use too many medicines					
2. Doctors place too much trust on medicines					
3. If doctors had more time with patients, they would prescribe fewer medicines					
4. Natural remedies are safer than medicines					
5. Medicines do more harm than good					
6. People who take medicines should stop their treatment for a while every now and then					
7. Most medicines are addictive					
8. All medicines are poisons					

	Strongly disagree	disagree	uncertain	agree	Strongly agree
9. my health, at present, depends on my medicine					
10. having to take my medicine worries me					
11. my life would be impossible without my medicine					
12. I sometimes worry about long term effects of my medicine					
13. without my medicine I would be very ill					
14. my medicine is a mystery to me					
15. my health in the future will depend on my medicine					
16. my medicine disrupts my life					
17. I sometimes worry about becoming too dependent on my medicine					
18. my medicine protects me from becoming worse					

Beliefs about Medicines Questionnaire (BMQ Specific-10 & BMQ General-8)©

Annex 16. Physician Questionnaires

A. Unified Parkinson's Disease Rating Scale (UPDRS)

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems.
Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place.
Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements
or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight;
could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression

0 = None.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING *(for both "on" and "off")*

5. Speech

0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.
1 = Rare choking.
2 = Occasional choking.

3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION
18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression;
lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair
(Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons.

Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal.
Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY *(In the past week)*
A. DYSKINESIAS
32. Duration: What proportion of the waking day are dyskinesias present?
(Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias?
(Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS
36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS
40. Does the patient have anorexia, nausea, or vomiting?
0 = No

1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING
STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

B. Non-Motor Symptoms Scale for Parkinson's Disease (NMSS)

Non-Motor Symptom assessment scale for Parkinson's Disease

Patient ID No: _____ **Initials:** _____ **Age:** _____

Symptoms assessed over the last month. Each symptom scored with respect to:

Severity: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient;
2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week);
4 = Very Frequent (daily or all the time).

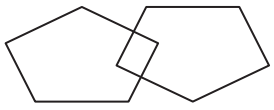
Domains will be weighed differentially. Yes/ No answers are not included in final frequency x severity calculation.
(Bracketed text in questions within the scale is included as an explanatory aid).

	Severity	Frequency	Frequency x Severity
Domain 1: Cardiovascular including falls			
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐
Domain 2: Sleep/fatigue			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading)	☐	☐	☐
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	☐	☐	☐
5. Does the patient have difficulties falling or staying asleep?	☐	☐	☐
6. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	☐	☐	☐
SCORE:			☐
Domain 3: Mood/cognition			
7. Has the patient lost interest in his/her surroundings?	☐	☐	☐
8. Has the patient lost interest in doing things or lack motivation to start new activities?	☐	☐	☐
9. Does the patient feel nervous, worried or frightened for no apparent reason?	☐	☐	☐
10. Does the patient seem sad or depressed or has he/she reported such feelings?	☐	☐	☐
11. Does the patient have flat moods without the normal "highs" and " lows"?	☐	☐	☐
12. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	☐	☐	☐
SCORE:			☐
Domain 4: Perceptual problems/hallucinations			
13. Does the patient indicate that he/she sees things that are not there?	☐	☐	☐
14. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	☐	☐	☐
15. Does the patient experience double vision? (2 separate real objects and not blurred vision)	☐	☐	☐
SCORE:			☐

C. Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Instructions for administration and scoring of the MMSE

Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the

sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.

- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Sources:

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Annex 17. Study Protocol Signature page

AbbVie Inc. (AbbVie)

Post Marketing Observational Study

Protocol (P16-831)

COSMOS - COmedication Study assessing Mono- and cOmbination therapy with levodopa-carbidopa inteStinal gel

Approved by:

[redacted]

16/JUN/17
Date

16/JUN/17
Date

23 JUN 2017
Date

19JUN2017
Date

16/Jun/17
Date