Statistical Analysis Plan

Study title:	**COSMOS** - **CO**medication **S**tudy assessing **M**ono- and c**O**mbination therapy with levodopa-carbidopa inte**S**tinal gel
Study identifier:	P16-831
Type of study:	Observational medical research
Name of test drug:	-
Active substance:	-
Indication studied:	Advanced Parkinson's disease
Sponsor:	AbbVie
Phase of study:	-
Author:	Dr. [redacted]
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Signatures

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List of abbreviations

ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
APD	Advanced Parkinson's disease
AUDD	Authorization for use/Disclosure of data
BMQ	Beliefs Medication Questionnaire
CSAI	Continuous subcutaneous apomorphine infusion
DBS	Deep brain stimulation
eDRF	Electronic data recording form
FAS	Full analysis set
FOG	Freezing of gait
HCRU	Healthcare Resource Utilization
ICD	Impulsive compulsive disorder
ICF	Informed consent form
LAR	Legal authorized representative
LCIG	Levodopa-carbidopa intestinal gel
LEDD	Levodopa equivalent daily dose
MedDRA	Medical dictionary for regulatory activities
MMSE	Mini-Mental State Examination
NMSS	Non-Motor Symptoms Scale for Parkinson's Disease
PD	Parkinson's disease
PDQ-8	Parkinson's Disease Quality of Life Questionnaire
PDSS-2	Parkinson's Disease Sleep Scale-2
PEG-J	Percutaneous endoscopic gastrostomy- with jejunal extension
PMOS	Post Marketing Observational Study
PRO	Patient reported outcome
QC	Quality control
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical analysis system
SD	Standard deviation
UPDRS	Unified Parkinson's Disease Rating Scale

1 Study protocol and scope

This statistical analysis plan (SAP) describes the final analysis of "COSMOS".
It is based on the final version of the protocol (no. P16-831), dated 14 June 2017, and on Administrative change no. 1, dated 02 November 2017.

2 General definitions and procedures

2.1 Software

Data entry is performed by means of the electronic data recording form (eDRF) system secuTrial®. Statistical analyses will be carried out with the SAS® package (version 9.4).

2.2 Coding

Coding will be performed by the medical advisor. The codes will be added to the exported study database in SAS.

MedDRA (English version) will be used for coding of medical history, adverse events and product complains.

For the coding system the latest available version at the time of coding start will be used.
PD (Parkinson's disease) medication and concomitant medication (for indications secondary to PD) will not be coded.

2.3 Procedures prior to statistical analysis

After completion of check of all available study data, the database will be closed. Data Management ensures that no data modifications are possible by Biostatistics within this database. Thereafter, only the responsible data manager and the project statistician will be privileged to have access to the database. Any changes to the analyses after the SAP has been finalized will be clearly described in the study report.

After database closure the data will be transferred electronically to the statistical software package SAS® data set format for statistical analysis. The SAS® data sets will be considered as source data sets for statistical analysis.

2.4 Reporting standard

A report for this analysis will be generated based on AbbVie standards. The report format is based on PMOS Study Results Report (Template_[study_]-pmos-results-rpt.docx) using relevant sections of the respective PMOS Study Result Report - Preparation Guide, version 03, June 2017. Sections that are not relevant to an epidemiological study will be removed.

2.5 Quality control

The SAP is consistent with the underlying study protocol. If there is a need for deviating substantially from the protocol-defined analysis, this is described in detail. The methods described in this SAP are mandatory for statistical programming.

Quality control (QC) of statistical programming will be performed according to the QC plan, which specifies all planned actions to ensure that the performed analyses are correct, traceable and in line with the planned analysis as specified in the SAP. The QC plan also includes filing of statistical programs, outputs and documentation of QC. It is finalized by the project statistical programmer before the start of any programming activities.

Documentation of QC is filed in the trial master file.

3 Study objectives

The study objectives are the following:

3.1 Primary objective

The primary objective of the study is to evaluate the percentages of Advanced PD patients on levodopa-carbidopa intestinal gel (LCIG) monotherapy right after LCIG initiation and at 3, 6, 9, and 12 months, respectively.

3.2 Secondary objectives

The secondary objectives of this study 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

4 Essential features of the study design

4.1 Type of study

This is a multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) of patients with APD (advanced Parkinson's disease) treated with LCIG in a routine clinical setting. It was planned to be conducted in approximately 15 countries.

4.2 Study population

Approximately 400 patients were to be included in the study. The study population consists of adult patients diagnosed with APD, on current treatment with LCIG, and treated with LCIG for at least 12 months prior to study inclusion.
The participating sites were to be hospitals or clinics experienced in treating patients with APD, and with experience in LCIG treatment. Participating physicians should have been involved in the respective patient's management since initiation of LCIG therapy. All eligible patients at a given site were to be enrolled consecutively in order to minimize selection bias.

4.2.1 Inclusion criteria

Patients were eligible for study participation if all of the following criteria were fulfilled:

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

4.2.2 Exclusion criteria

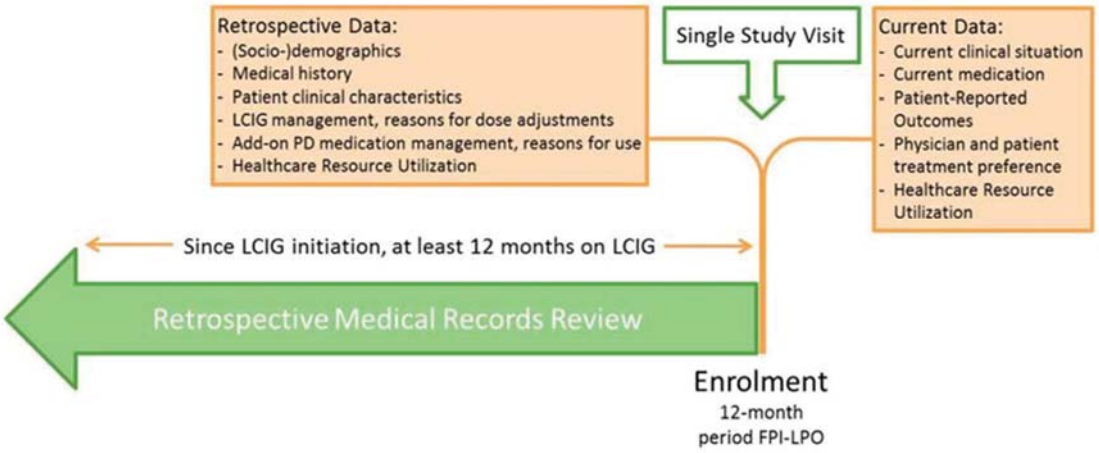
Patients with the following criteria were not eligible for study participation:

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

4.3 Study schedule

This study consists of one single visit. The observational period is mainly retrospective and includes one cross-sectional study visit. Data gathered were derived from the time prior to initiation of LCIG therapy until the day of the study visit (see Figure 4-1). Patients were enrolled starting from 14 December 2017.

Figure 4-1: Study schematic



4.4 Methods of measurement and documentation

Patient data and site characteristics were to be documented on the eDRF. In addition, patients were asked to complete the following questionnaires: Parkinson's Disease Quality of Life Questionnaire (PDQ-8), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS), Parkinson's Disease Sleep Scale-2 (PDSS-2), and Beliefs Medication Questionnaire (18-item BMQ). Physicians should complete the following questionnaires: Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale for Parkinson's Disease (NMSS), Mini-Mental State Examination (MMSE), and Healthcare Resource Utilization Questions (HCRU). Data from questionnaires were also to be recorded on the eDRF.

An overview of activities and procedures is given in Table 4-1.

Table 4-1: Activities and procedures

Activity/Procedure	Before LCIG initiation	LCIG initiation	During LCIG treatment	Patient visit
	Retrospective data from patient files			
Center characteristics	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			
Add-on PD medication since LCIG initiation		X	X	X
Clinical PD status	X	X		
LCIG infusion data		X	X	X
Concomitant Medication (for indications secondary to PD)	X	X	X	X
Behaviour/mentation/mood (UPDRS Part I)	X			X
Activities of daily living (UPDRS Part II)	X			X
Motor examination (UPDRS Part III)	X			X
Treatment complications (UPDRS Part IV)	X			X
Disease Stage (Modified Hoehn & 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 (HCRU)				X
Beliefs Medication (BMQ)				X
Adverse Events / Adverse Reactions / Product complaint		X	X	X

In detail the following information was documented:

4.4.1 Site information

For each site information was to be documented in the eDRF comprising type of site, origin of service, average number of PD and APD patients per year, average frequency of visits for APD patients on device aided therapy, number of specialist physicians working with PD patients, support services/functions available at the site, access to invasive treatments.

4.4.2 Physician's profile

The physician was 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 (Deep brain stimulation) or CSAI (Continuous subcutaneous apomorphine infusion).

4.4.3 Patient data

The following patient data were to be recorded in the eDRF:

- Patient demographics and socio-demographics

- Medical history and PD history
- Previous PD medication and add-on PD treatment during LCIG treatment
- Concomitant disease and medication
- LCIG treatment
- Clinical PD status

4.4.4 Patient reported outcomes (PROs)

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

Using 8 items patients were asked to state how often they had encountered certain problems during the last month using the following rating scale: Never (0), occasionally (1), sometimes (2), often (3), always or cannot do at all (4).

Each of the eight items will be evaluated separately as a score ranging from 0 to 100. Thus, the score for each item will be calculated as the respective value divided by 0.04.

The *PDQ-8 summary index* will be analyzed and is derived as the sum of the single items divided by 0.32. Like that, the PDQ-8 summary index is normalized to take values between 0 and 100. In case of missing items the PDQ-8 summary index will not be calculated.

A higher score/summary index indicates a higher impairment of quality of life.

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 (ICDs) which may occur in PD patients under dopaminergic drug therapy.

QUIP-RS uses a 5-point Likert scale upon which each symptom is rated based on frequency (Never (0), Rarely (1), Sometimes (2), Often (3), Very often (4)). There are four primary questions, related to the 4 ICDs (compulsive gambling, buying, eating, and sexual behavior), and 3 related disorders (medication use, punding, and hobbyism). The total QUIP-RS score ranges from 0 to 112.

The following scores will be auto calculated in the eCRF, each as sum of the respective categories:

1. Compulsive gambling
2. Sexual behavior
3. Buying
4. Eating
5. Hobbyism-Punding
6. PD medication
7. Total ICD scores (1.- 4.)
8. Total QUIP-RS score (1.- 6.)

A higher score denotes greater severity.

Parkinson's Disease Sleep Scale-2 (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. 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 (items 4, 5, 6, 12, 13), PD symptoms at night (items 7, 9, 10, 11, 15), and disturbed sleep (items 1, 2, 3, 8, 14).

The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 to 4). Scores are calculated as sum of the respective items for each domain. In addition, a total score summing up all items will be calculated. The scores can only be calculated if no contributing item is missing. Higher scores denote a poorer sleep quality.

Beliefs Medication Questionnaire (BMQ)

The BMQ consists of 18 items and is a tool for screening patients' beliefs, attitudes and concerns regarding their medication. For each of the 18 items a 5-point Likert scale is used ranging from 1 (strongly disagree) to 5 (strongly agree).

The BMQ 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. The general section is sub-divided into two sub-scales: General-Overuse (items 1-4) and General-Harm (items 5-8). The specific section is subdivided into the two sub-scales Specific-Necessity (items 9, 11, 13, 15, 18) and Specific-Concern (items 10, 12, 14, 16, 17). For each sub-scale a score will be calculated as average of the contributing items. The scores can only be calculated if no contributing item is missing.

Higher values of the General-Overuse score indicate a stronger belief that doctors overuse medicines in general. Higher values of the General-Harm score indicate a stronger belief in harm of medicines in general.

Higher values of the Specific-Necessity score indicate a greater perceived necessity of the specific treatment. Higher values of the Specific-Concerns score indicate greater perceived concerns about the specific treatment.

4.4.5 Questionnaires reported by physicians

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is an investigator-used tool to follow the longitudinal course of Parkinson's disease. It includes the five 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 scores of the sections part I, part II, part III and part IV as well as the UPDRS total score (total core range 0-199) will be auto calculated in the eCRF.

The sub-scores of part IV will not be auto calculated. Each of these three sub-scores (Dyskinesias and Dystonia, Motor fluctuations, Other complications) will be calculated as the sum of the contributing items.

A sub-score will only be calculated if none of the contributing items is missing. A higher score always indicates a higher impairment.

In addition to the original UPDRS items the duration of dyskinesia and the off period duration were recorded along with item 32 and 39, respectively.

In addition to the scores, the single items 32, 33, 34, 35 and 39 will be analyzed separately (see Section 6.3), including the additionally requested duration of dyskinesia (item 32) and the duration of off period (item 39).

Rating scale part V (Modified Hoehn & Yahr Stage):

UPDRS V consists of one question on the stage of disease. This staging is based on evaluation of PD symptoms, progress and relative level of disability. The UPDRS V score ranges from 0 to 5 with scores of whole numbers as well as 1.5 and 2.5. A higher score indicates a higher stage of disease.

Non-Motor Symptoms Scale for Parkinson's Disease (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 encompass 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 including falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous [pain, taste/smell, weight change, excessive sweating].

The scores of the 9 domains as well as the total score will be auto calculated in the eCRF. The total NMSS score ranges from 0 to 360 with a higher score indicating a higher level of non-motor symptoms burden.

Mini-Mental State Examination (MMSE)

The MMSE is a brief, 30-point questionnaire, 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.

The total MMSE score will be auto calculated in the eCRF.

Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (0 –17 points) or mild (18 – 23 points) cognitive impairment.

Healthcare Resource Utilization Questions (HCRU)

The HCRU questionnaire contains questions on the occupational status, nursing home visits, hospitalizations/emergency care visits, caregiver support, and other items with respect to healthcare resource utilization. Ten of the questions the neurologist should discuss with each patient and record the patient's responses. Four questions should be answered by the physician. Each question will be analyzed separately.

4.4.6 Adverse event reporting

The physicians were asked to report product complaints, pregnancies, all adverse events occurring after the time of patient authorization, and all adverse reactions (i.e. adverse events considered as likely related to an Abbvie product) with onset dates prior to patient authorization.

5 Analysis data set

One analysis set will be used:

The full analysis set (FAS) consists of all patients enrolled who fulfill the patient selection criteria.

6 Variables for analysis

6.1 Site information

- Institution type
- Origin of service
- Average number of PD and APD patients per year
- Average frequency of routine visits for APD patients on device aided therapy
- Number of specialist physicians working with PD patients
- Support services/functions available at the site (multiple answers)
- Access to invasive treatments (multiple answers)

6.2 Physician's profile

- Therapeutic specialty (type)
- Number of years physician has been working at the institution
- Approximate number of PD patients treated per year
- Approximate number of APD patients treated per year
- Approximate number of APD patients treated with LCIG per year
- Use of standard treatment algorithms/established guidelines/definitions of PD treatment (yes, no)
    - If yes: specification (multiple answers)
- Overall treatment preference
- Years of DBS experience
- Number of DBS patients
- Years of CSAI experience
- Number of CSAI patients

- Years of LCIG experience

6.3 Patient data

Patient disposition

- Patients enrolled / in FAS (yes, no)
- Patients fulfilling all selection criteria (yes, no)
    - If no: List of patients violating any selection criteria

Demographics

- Age calculated as year of visit minus year of birth
- Gender
- Race
- Education
- Residence of the patient

Parkinson's disease history

- Time since PD diagnosis calculated as year of visit minus year of PD diagnosis + 1
- Age at PD diagnosis calculated as year of PD diagnosis minus year of birth
- PD motor phenotype
- Time from PD diagnosis to motor fluctuation onset calculated as year of motor fluctuation onset minus year of PD diagnosis +1
- Time from PD diagnosis to start of LCIG calculated as year of first start date of LCIG initiation minus year of PD diagnosis +1
- Morning akinesia (yes, no)
    - If yes: time from PD diagnosis to onset of morning akinesia calculated as year of onset of morning akinesia minus year of PD diagnosis +1
- Wearing off (yes, no)
    - If yes: time from PD diagnosis to onset of wearing off calculated as year of onset of wearing off minus year of PD diagnosis +1
- Dyskinesia present (yes, no)
    - If yes: time from PD diagnosis to onset of dyskinesia calculated as minus year of onset of dyskinesia minus year of PD diagnosis +1

Clinical PD status immediately prior to / at LCIG initiation

- Duration of 'Off' state time during a 24h period (hours)
- Duration of dyskinesia during a 24h period (hours)
- Severity of dyskinesia
- Reason for LCIG start (multiple answers)
- Conduction of Nasojejunal test phase (yes, no)
    - If yes: reason (multiple answers)
    - If no: reason (multiple answers)
- Duration of titration calculated as date of titration finalization minus date of titration initiation +1
- Duration of LCIG treatment calculated as visit date minus date of LCIG initiation start +1
- Hospitalization for titration and PEG-J placement (yes, no)
- Hospitalization for PEG-J placement (yes, no)

Motor symptoms

Separately for 'immediately prior to LCIG initiation' and 'visit':

- Number of motor symptoms
- Number of motor symptoms in appropriate categories
- Bradykinesia (yes, no, unknown)
    - If yes: Severity
      Frequency
- Rigidity (yes, no, unknown)
    - If yes: Severity
      Frequency
- Tremor (yes, no, unknown)
    - If yes: Severity
      Frequency
- Dystonia / cramps (yes, no, unknown)
    - If yes: Severity
      Frequency
- Gait Impairment (except freezing of gait (FOG); yes, no, unknown)
    - If yes: Severity
      Frequency
- Balance problems (yes, no, unknown)
    - If yes: Severity
      Frequency
- Hypophonia (yes, no, unknown)
    - If yes: Severity
      Frequency
- Dysphagia (yes, no, unknown)
    - If yes: Severity
      Frequency
- Nocturnal/morning akinesia (yes, no, unknown)
    - If yes: Severity
      Frequency
- Freezing of gait (FOG; yes, no, unknown)
    - If yes: Severity
      Frequency
- Other (yes, no)
    - If yes: List of symptoms

Non-motor symptoms

Separately for 'immediately prior to LCIG initiation' and 'visit':

- Number of non-motor symptoms
- Number of non-motor symptoms in appropriate categories
- Anxiety (yes, no, unknown)
    - If yes: Severity
      Frequency
- Pain (yes, no, unknown)
    - If yes: Severity
      Frequency

- Cognitive Impairment (yes, no, unknown)
  - If yes: Severity
    Frequency
- Depression (yes, no, unknown)
  - If yes: Severity
    Frequency
- Apathy (yes, no, unknown)
  - If yes: Severity
    Frequency
- Fatigue (yes, no, unknown)
  - If yes: Severity
    Frequency
- Urinary symptoms (yes, no, unknown)
  - If yes: Severity
    Frequency
- Constipation (yes, no, unknown)
  - If yes: Severity
    Frequency
- Orthostatic hypotension (yes, no, unknown)
  - If yes: Severity
    Frequency
- Other (yes, no)
  - If yes: List of symptoms

Symptoms related to treatment

Separately for 'immediately prior to LCIG initiation' and 'visit':

- Number of symptoms related to treatment
- Number of symptoms related to treatment in appropriate categories
- Hypersexuality (yes, no, unknown)
  - If yes: Severity
    Frequency
- Compulsive shopping (yes, no, unknown)
  - If yes: Severity
    Frequency
- Gambling (yes, no, unknown)
  - If yes: Severity
    Frequency
- Binge Eating (yes, no, unknown)
  - If yes: Severity
    Frequency
- Punding (yes, no, unknown)
  - If yes: Severity
    Frequency
- Dopamine Dysregulation syndrome (yes, no, unknown)
  - If yes: Severity
    Frequency
- Other (yes, no)

- Total number of symptoms calculated as sum of the number of motor symptoms, number of non-motor symptoms and number of symptoms related to treatment

Co-morbidities

Separately for 'immediately prior to LCIG initiation' and 'visit':

- Any major co-morbidity (yes, no)
- Co-morbidities (multiple answers)
- For each co-morbidity:
  - If ticked: relation to PD (yes, no)
  - Additionally if 'Cognitive dysfunction' ticked: Severity
- If 'Other' co-morbidity ticked: Specification (MedDRA coded)

Historical therapy discontinued prior to considering LCIG initiation

- Any device aided therapy other than LCIG in the past (yes, no)
  - If yes: Therapy (multiple answers)
    Separately for DBS and Apomorphine:
    - Duration: over all entries the treatment duration (end date minus start date +1) will be summarized
    - Reason for discontinuation (multiple answers)
- Any dopamine agonists in the past (yes, no)
  - If yes: Therapy (multiple answers, patient based)
    Separately for each therapy:
    - Duration: over all entries the treatment duration (end date minus start date +1) will be summarized
    - Reason for discontinuation (multiple answers)

Separate lists of other medications and therapies only for indications secondary to PD will be provided for:

- before LCIG initiation
- after LCIG initiation
- at LCIG initiation
- at 12 months after LCIG initiation
- at study visit

Patient reported outcomes (PROs)

- PDQ-8: Eight single items
  PDQ-8 summary index
- QUIP-RS: Compulsive gambling
  Sexual behavior
  Buying
  Eating
  Hobbyism-Punding
  PD medication
  Total ICD scores
  Total QUIP-RS score

- PDSS-2: Motor symptoms at night
  PD symptoms at night
  Disturbed sleep
  Total PDSS-2 score
- BMQ: General-Overuse
  General-Harm
  Specific-Necessity
  Specific-Concern

Questionnaires reported by physicians

- UPDRS (separately for 'prior to LCIG initiation' and 'patient visit if available'):
  Part I
  Part II
  Part III
  Part IV
    - Dyskinesias and Dystonia
    - Motor fluctuations
    - Other complications
    - Depending on data quality: Dyskinesias duration during waking day in hours (from item 32)
    - Dyskinesias duration during waking day in categories (item 32)
    - Severity of dyskinesia (item 33)
    - Pain related to dyskinesia (item 34)
    - Early morning dystonia (item 35)
    - 'Off' state time during waking day in hours (from item 39)
    - 'Off' state time during waking day in categories (item 39)

  Part V
- NMSS: Nine domain scores
  Total NMSS score
- Total MMSE score (separately for 'prior to LCIG initiation' and 'patient visit' if available)

6.4 Primary variable

There are two primary variables:

1. LCIG monotherapy 1 (yes, no) at LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation

   with the following definition:

   LCIG monotherapy means that the patient is not on any add-on PD medication or PD therapy at the respective time point.

2. LCIG monotherapy 2 (yes, no) at LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation
   with the following definition:
   LCIG monotherapy means that the patient is allowed to take an add-on PD medication or PD therapy at the respective time point, however, only in the evening after the LCIG infusion is completed (i.e. reason for start of add-on PD medication: other).

Additional specifications for both variables are:

- Medications for indications secondary to PD are allowed.
- If the reason for add-on PD medication is missing the medication will be considered as taken during LCIG infusion (i.e. no monotherapy).
- LCIG initiation date is the start date of the first LCIG infusion.
- 3 months after LCIG initiation is calculated as LCIG initiation date + rounded (3 [months] x 30.4 [days]). 6, 9, and 12 months after LCIG initiation will be calculated analogously.
- For LCIG initiation date with missing day the 15th will be used.

6.5 Secondary variables

Descriptive data from patient's PD medication

- Add-on PD medication:

  At the time points LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation, at visit and at appropriate time points between 12 months after LCIG initiation and the visit:

  - Add-on PD medication (multiple answers; category and medication/therapy; patient based)
    Category and medication/therapy are as follows:

Category	Medication/therapy
Levodopa	Levodopa/carbidopa Levodopa/benserazide Levodopa/carbidopa/entacapone Other
COMT inhibitor	Entacapone Tolcapone Opicapone Other
Dopamine Agonist (excluding Apomorphine)	Pramipexole Ropinirole Cabergoline Rotigotine Other
MAO Inhibitor	Selegiline Safinamide Rasagiline Other
NMDA Antagonist	Budipine Amantadine Other
Apomorphine	Apomorphine intermittent injection SC Apomorphine subcutaneous continuous infusion 30mg/ml solution Other
Anticholinergics	Anticholinergics Other

Surgical therapy	Pallidotomy Thalamotomy Deep brain stimulation (DBS) Stem Cell Transplant Other
Other	-

  - Total daily dose separately for each category and for each medication/therapy (except all 'Other', Anticholinergics, and Surgical therapy; Apomorphine only if possible)
  - Levodopa equivalent daily dose (LEDD) separately for each category and for each medication/therapy if applicable (see Section 7.6)
  - Total daily LEDD (in mg; see Section 7.6)
  - Posology (i.e. average number of intakes per day) separately for each category and for each medication/therapy (except all 'Other' and Surgical therapy)
  - Add-on PD medication in categories and medication/therapy (multiple answers)
- LCIG infusion:
  At the time points LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation, at visit and at appropriate time points between 12 months after LCIG initiation and the visit:
  - Total dose per day (in ml) with total dose per day calculated as morning dose + continuous dose x duration of infusion + extra dose.
  - Morning dose (in ml)
  - Continuous dose (in ml/h)
  - Daily duration of infusion (in h/day)
  - Daily duration of infusion in the following categories:
    - 0 - <16 h/day
    - 16 - <24h/day
    - 24h/day

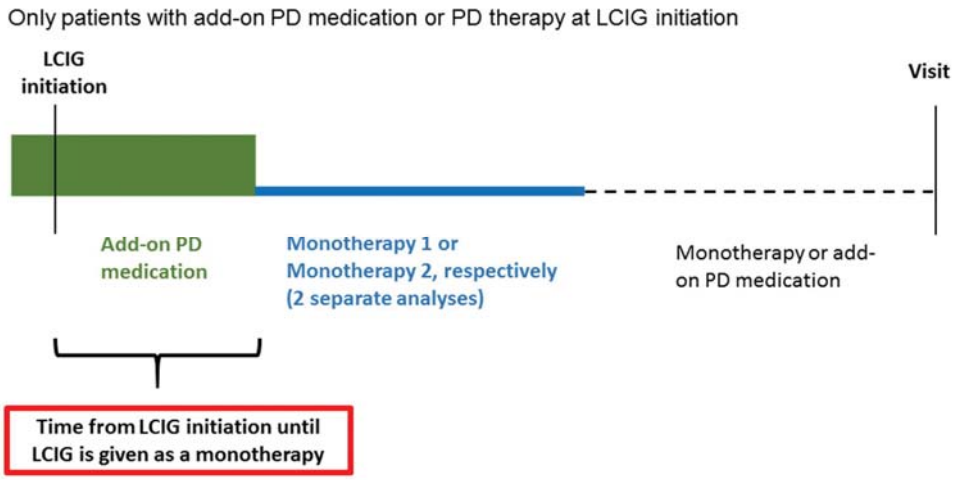
    For patients with a daily duration of 24h/day the dosing information will be listed

- Tapering process:
  - For each add-on PD medication/therapy over all treatment phases:
    - Minimum total daily dose; if the add-on PD medication is stopped, the minimum total daily dose will be set to 0
    - Maximum total daily dose
    - The tapering process is any change in the dose concentration (decreasing or increasing dose) and the number of days for tapering process is the number of days between maximum and minimum daily dose; patients with minimum (or maximum, respectively) daily dose not at the end of the tapering process will be checked. A maximum duration of ca. 2 months of the tapering process is allowed (otherwise the tapering process is set to missing). Dates which are incomplete will not be imputed and, thus, no tapering process can be identified (missing). If the add-on PD medication is stopped, but no entry with

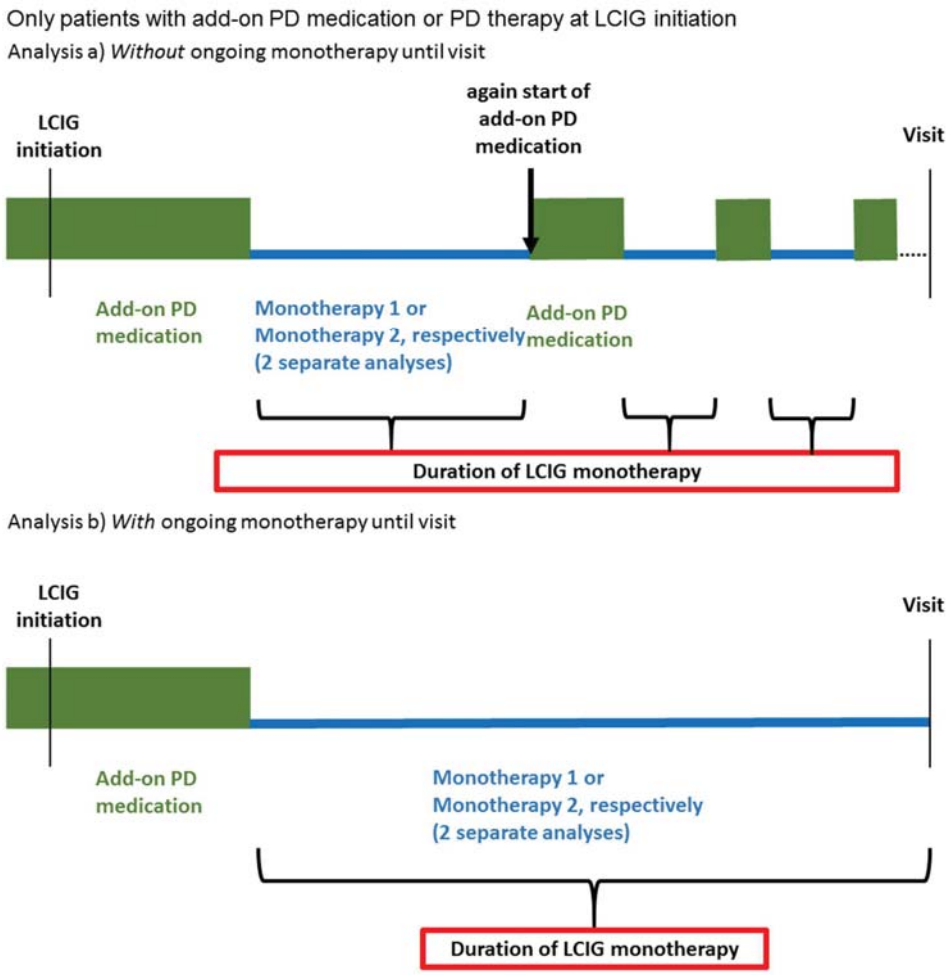
dose = 0 is recorded the stop date will be used as date of minimum total daily dose.

- For each add-on PD medication/therapy:
  Only for the time period of tapering process:
  If within the tapering process: at the time points LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation and at visit:
  - Total daily dose (except all 'Other', Anticholinergics, and Surgical therapy; Apomorphine only if possible)
  - Posology (i.e. number of intakes per day; except all 'Other' and Surgical therapy)

- Reasons:
  - For each add-on PD medication/therapy at the time points LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation and at visit::
    - Reason for start (multiple answers)
    - If not ongoing: reason for discontinuation (multiple answers)
  - Reason for change on LCIG dose in general
  - Reason for LCIG dose changes (multiple answers) by 5%, 10%, 15%, 20% or 25% or higher
  - Reason for substantial LCIG dose changes (multiple answers) with substantial change defined as any increase or decrease of the total daily LCIG dose by more than 20%
- Latency and duration of treatments:
  - For patients with add-on PD medication or PD therapy at LCIG initiation: Time from LCIG initiation until LCIG is given as a monotherapy (separately for monotherapy 1 and monotherapy 2 definition)



  - For patients with add-on PD medication or PD therapy at LCIG initiation and separately for patients with and without ongoing monotherapy at visit: Duration of LCIG monotherapy (separately for monotherapy 1 and monotherapy 2 definition)



  - For each add-on PD medication/therapy:
    Time from LCIG initiation until the respective add-on PD medication/therapy is started or changed
  - Time from LCIG initiation until the first LCIG dose change by 5%, 10%, 15%, 20% or 25%
  - Time from LCIG initiation until the first substantial LCIG dose change with substantial change defined as any increase or decrease of the total daily LCIG dose by more than 20% in relation to first LCIG infusion

- LCIG monotherapy (1 and 2) vs. LCIG plus add-on PD medication:
  - HCRU:
    - Primary occupation (retired, on sick leave, unemployed, working full time, working part-time, student)
      - If retired: due to PD (yes, no)
      - If on sick leave: due to PD (yes, no)
      - If unemployed: due to PD (yes, no)
    - Permanent living in a nursing home/institution (yes, no)
    - Help in daily activities
    - Frequency of visits:
      - General practitioner

- Nurse
- Occupational/speech therapist
- Physiotherapist
- Psychologist and/or psychiatrist
- Dietician

- Discussion of LCIG monotherapy (yes, no, patient did not remember)
- Offering of LCIG monotherapy (yes, no, patient did not remember)
- Number of pills in addition to LCIG the patient would be willing to take each day
- Problems before starting LCIG (multiple answers)
- Help required to remember to take the medication (yes, no)
- Influence on the patient's decision to start treatment with LCIG (yes, no, missing)
  - If not 'no':
    - Doctor
    - Caregiver
    - Other family member
- Any scheduled visits with the treating physician for PD (yes, no)
- Any extra or unscheduled visits with the treating physician for PD (yes, no)
- Been seen in the Emergency Room due to PD (yes, no)
- Hospitalization (yes, no)
  - If yes: due to PD (yes, no)

- Overall treatment preference from physician's profile (LCIG as monotherapy, LCIG plus add-on PD medication)

6.6 Reportable events and product complaints

- Separately for 'LCIG initiation' and 'LCIG Maintenance Treatment':
  - Any adverse reaction (yes, no; patient based)
  - Event diagnosis (MedDRA coding; patient based)
  - Action taken (event based)
- Events occurring after the time of patient authorization:
  - Reportable event (patient based):
    - Any adverse event (AE)
    - Serious adverse events (SAE)
    - Adverse drug reaction (ADR)
  - Event diagnosis (MedDRA coding; patient based): separately for AE, SAE, ADR
  - Any pregnancy which has not been reported to an AbbVie care Duodopa nurse (yes, no)
  - Any product complaint that has not been reported before (yes, no)
    - If yes: Complaint description (MedDRA coding; patient based)

6.7 Missing data and outliers

The handling of missing single items in rating scales is described in Sections 4.4.4 and 4.4.5.

7 Statistical methodology

7.1 General methodology

All statistical analyses will be carried out by means of the SAS® package (version 9.4).

Quantitative data (e.g. age) will be described by the statistical parameters valid N, missing N, mean, standard deviation (SD), minimum, the 25%-quartile, median, the 75%-quartile, and the maximum.

Qualitative data (e.g. gender) will be presented by means of (absolute and relative) frequency distributions. If applicable, two methods will be followed for calculation of percentages. The first method considers missing data as a separate group, which results in the same sample size for all parameters. The second method of calculation is based on the valid data per parameter, excluding patients with missing values ("valid data analysis"). Accordingly, this results in different sample sizes. In general, description of results within the report refers to the "valid data analysis".

For categorical variables associated with score values, the mean will be calculated as well.

Two-sided 95% confidence intervals will be provided for the primary, and if applicable, the secondary variables defined by proportions.

Statistical methods which differ from the above mentioned methods or require further description will be addressed in the following sections.

7.2 Site information

The number of participating sites (e.g. sites with at least one patient) and a summary of characteristics of the sites will be presented (see Section 6.1).

7.3 Physician's profile

The characteristics of the participating physicians will be presented (see Section 6.2).

7.4 Patient data

Patient disposition will be evaluated for all patients enrolled.

All other variables will be evaluated for FAS according to the methods described in Section 7.1.

Patient data will be analyzed overall and separately for the following three groups:

- Patients on monotherapy 1 at 12 months after LCIG infusion (see Section 6.4)
- Patients on monotherapy 2 at 12 months after LCIG infusion (see Section 6.4)

Patients not on monotherapy 2 at 12 months after LCIG infusion (see Section 6.4) For duration of 'Off' state (hours) and duration of dyskinesia (hours) the difference will be calculated between the time points 'prior to LCIG initiation' and visit (UPDRS IV: modified items 39 and 32) as value at visit minus value prior to LCIG initiation.

'Other' co-morbidities will be coded using MedDRA. Incidence rates will be calculated with respect to System Organ Class and Preferred Term.

Regarding the 'Historical therapy discontinued prior to considering LCIG initiation' patient based means that a therapy type will only be counted once per patient.

A list of other medications and therapies only for indications secondary to PD will be provided including the following information:

- PatientID
- Name of concomitant medication or therapy
- Indication
- Total daily dose
- Dose unit
- Start date
- End date
- Ongoing at the end of study

7.5 Primary variable

The primary variable will be evaluated for FAS.

For the time period between 12 months after LCIG initiation and the visit, appropriate time points will be used.

7.6 Secondary variables

The secondary variables will be evaluated for FAS.

Secondary variables will be analyzed overall and separately for the following three groups:

- Patients on monotherapy 1 at 12 months after LCIG infusion (see Section 6.4)
- Patients on monotherapy 2 at 12 months after LCIG infusion (see Section 6.4)
- Patients not on monotherapy 2 at 12 months after LCIG infusion (see Section 6.4)

Regarding 'Add-on PD medication' patient based means that a therapy type will only be counted once per patient. The variables total daily dose, LEDD and posology will additionally be analyzed per category by summing up the values of the corresponding medication/therapy.

Regarding total dose per day the difference will be calculated between the time points LCIG initiation start, 12 months after LCIG initiation start and visit as follows:

- Total dose per day at 12 months after LCIG initiation start minus total dose per day at LCIG initiation start
- Total dose per day at visit minus total dose per day at LCIG initiation start
- Total dose per day at visit minus at 12 months after LCIG initiation start

If applicable, levodopa equivalent daily dose (LEDD) will be calculated separately for each medication/therapy as total daily dose in mg multiplied with the respective factor (from Table 7-1; [1], [2], [3]). Exceptions are entacapone, tolcapone and opicapone: irrespective of the entacapone dose (or tolcapone or opicapone dose, respectively) the corresponding levodopa dose is multiplied by the given factor. This will then be considered as LEDD for entacapone (or tolcapone or opicapone, respectively).

The total daily LEDD will be the sum over all daily LEDDs which were calculated separately for each medication at the respective time point.

Table 7-1: Factor for levodopa equivalent daily dose

Medication	**Factor**
Levodopa/carbidopa	1.11
Levodopa/benserazide	1
Levodopa/carbidopa/entacapone	1.33
Amantadine	1
Apomorphine	10
Cabergoline	80
Entacapone	concomitant levodopa multiplied by 0.33
Tolcapone	concomitant levodopa multiplied by 0.5
Pramipexole	100
Rasagiline	100
Ropinirole	20
Rotigotine	30
Selegiline oral	10
Opicapone	concomitant levodopa multiplied by 0.65
Safinamide	
Budipine	5

7.7 Reportable events

Reportable events will be coded using MedDRA and evaluated for FAS. Incidence rates will be calculated with respect to System Organ Class and Preferred Term.

Details of reportable events will be listed including the following information:

- PatientID
- Onset date
- End date
- Ongoing at the end of study
- Event diagnosis (MedDRA coding)
- Action taken
- Severity
- Relationship to LCIG
- Serious adverse event (no/yes)

7.8 Regression analyses

For the application of regression analysis, missing/unknown data for prognostic factors are imputed. Imputation is planned to be accomplished by a regression based single imputation method where missing values of one predictor variable are predicted by regression models with a set of remaining potential prognostic variables as independent variables. This might require adequate preprocessing of the data. Modification of this imputation strategy is possible if implied by the data.

Regression analyses will be evaluated for FAS and conducted on imputed data.

Regression analyses will be performed separately for each of the two primary variables (see Section 6.4):

LCIG monotherapy 1 (LCIG monotherapy 2, respectively) at 12 months after LCIG initiation will be used as dependent (i.e. response) variable in two multivariable logistic regression models. The independent variables (i.e. potential predictors) will be checked for collinearity.

For the first multivariable logistic regression model the following variables will be considered as potential predictors (i.e. independent variables):

Table 7-2: Potential predictors used for regression analysis 1

Variable	Range	Dichotomization/Grouping
Age	numeric	-
Gender	Male, Female	Male vs. Female
Race	White, Black, Asian, Mixed, Other	White vs. Non-White
Education	No formal education, primary school, secondary school, non-university professional education, university	Less than secondary school vs. secondary school or higher
Total number of symptoms	numeric	
Number of symptoms related to treatment	numeric	
Number of motor symptoms	numeric	-
Number of non-motor symptoms	numeric	-
Total daily LEDD at LCIG initiation	numeric	-
Time from PD diagnosis to start of LCIG	numeric	-
Duration of 'Off' state time during a 24h period	numeric	-
Duration of dyskinesia during a 24h period	numeric	-
UPDRS V prior to LCIG initiation (if available)	numeric	-
Any device aided therapy other than LCIG in the past	Yes, No	Yes vs. No
Any dopamine agonists in the past	Yes, No	Yes vs. No
PD motor phenotype	Tremoric, Akinetic rigid, Mix	
Time from PD diagnosis to motor fluctuation	numeric	
Time from PD diagnosis to onset of morning akinesia	numeric	
Country		
GNI	numeric	

Categorical predictors will be dichotomized / grouped as shown in Table 7-2 in order to simplify interpretation.

Backward elimination with a significance level of 0.05 will be applied to stepwise automatically select relevant predictors. Effect estimates and p-values will be given for each (potential) predictor.

For the second multivariable logistic regression model the following variables will be considered as potential predictors (i.e. independent variables):

Table 7-3: Potential predictors used for regression analysis 2

Variable	Range	Dichotomization/Grouping
Approximate number of APD patients treated per year	numeric	-
Years of LCIG experience	numeric	-
Years of DBS experience	numeric	-
Approximate number of APD patients treated with LCIG per year	numeric	-
Number of years physician has been working at the institution	numeric	-
Average number of PD and APD patients per year at center	numeric	-
Number of specialist physicians working with PD patients at center	Numeric	-
Origin of service at center	National health services, Private health services	National health services vs. Private health services
Average frequency of routine visits for APD patients on device aided therapy at center	< 1x/year, 1x/year, 2x/year, 3x/year, > 3x/year	≤ 1x/year vs. ≥ 2x/year
Country		
GNI	numeric	

Categorical predictors will be dichotomized / grouped as shown in Table 7-3 in order to simplify interpretation.

Backward elimination with a significance level of 0.05 will be applied to stepwise automatically select relevant predictors. Effect estimates and p-values will be given for each (potential) predictor.

For both regression models the Gross National Income (GNI) is defined as follows (source: https://data.worldbank.org/indicator/NY.GNP.PCAP.CD):

Country	GNI
Austria	45.44
Bulgaria	7.76
Canada	42.87
Czech Republic	18.16
Croatia	12.43
Estonia	18.19

Greece	18.09
Hungary	12.87
Ireland	55.29
Israel	37.27
Netherlands	46.18
Romania	9.97
Spain	27.18
Sweden	52.59

7.9 Interim analysis

No interim analysis was conducted.

7.10 Further issues

Due to the exploratory character of the study, modifications and extensions of the pre-specified analyses are possible without constraints, if indicated by the data.

8 References

1. Tomlinson, C.L., et al., *Systematic review of levodopa dose equivalency reporting in Parkinson's disease.* Mov Disord, 2010. **25**(15): p. 2649-53.
2. Reichmann, H., *Budipine in Parkinson's tremor.* J Neurol Sci, 2006. **248**(1-2): p. 53-5.
3. Cervantes-Arriaga, A., et al., *Cálculo de unidades de equivalencia de levodopa en enfermedad de Parkinson.* Arch Neurocien (Mex), 2009. **14**(2): p. 116-119.