Title Page

Title	**A Retrospective Cohort Study for Estimating Incidence Rates of Infusion Site Events for ABBV-951 for the Treatment of Advanced Parkinson's Disease**
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Joint PASS	No
Research Question and Objectives	The overall aim of this study is to evaluate the effectiveness of additional risk minimization measures (aRMM) by estimating incidence rates of infusion site events (i.e., infusion site infections and/or serious infusion site reactions) in Parkinson disease (PD) patients exposed to ABBV-951 in real-world clinical practice, using data sources from Finland and France. The frequency of infusion site events observed in this real-world study will be interpreted in context of the predefined reference value which is the frequency of the infusion site events reported in the AbbVie clinical trial. The following objectives will be investigated among patients with advanced PD following initiation of treatment with ABBV-951: • To quantify the incidence rate of first infusion site events (first infusion site infection OR first serious infusion site reactions) • To quantify the incidence rate of first infusion site infection • To quantify the incidence rate of first serious infusion site reaction
Country(-ies) of Study	Finland and France
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This study will be conducted in compliance with this protocol.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	AbbVie Inc.
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1.0 Table of Contents

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2.0 Abbreviations

AE	Adverse event
aRMM	Additional risk minimization measures
ATC	Anatomical Therapeutic Chemical
AvoHILMO	Register of Primary Health Care Visits
CI	Confidence Interval
CNAM	Caisse Nationale d'Asssurance Maladie
COMT	Catechol-O-methyl transferase
EMA	European Medicines Agency
EMR	Finnish Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorization Studies
FDA	Food and Drug Administration
GVP	Good pharmacovigilance practices
HILMO	Care Register for Health Care
ICD	International Classification of Diseases
LCIG	Levodopa-carbidopa intestinal gel
LPD	Longitudinal Patient Database
MAO-B	Monoamine oxidase-B
NOMESCO	Nordic Medico-Statistical Committee
PASS	Post-authorization safety study
PD	Parkinson's disease
PEG-J	Percutaneous endoscopic gastrostomy with jejunal extension
PMSI	Programme de Médicalisation des Systèmes d'Information
QC	Quality control
RMM	Risk Minimization measure
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SNDS	Systeme National des Données de Santé
THL	(Finnish) National Institute for Health and Welfare

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4.0 Abstract

Title: A Retrospective Cohort Study Estimating Incidence Rates of Infusion Site Events with ABBV-951 for the Treatment of advanced Parkinson's Disease.

Rationale and Background: Parkinson's disease (PD) is a progressive disorder of the nervous system. As it progresses to more advanced stages, many patients become unable to manage their symptoms effectively with available oral medications. AbbVie has developed ABBV-951, which provides a 24-hour, continuous subcutaneous delivery of foscarbidopa and foslevodopa via an ambulatory infusion pump for the treatment of advanced PD. In the clinical trial, ABBV-951 was generally safe and well tolerated. Infusion site events including infusion site reactions and infusion site infections were observed due to the continuous subcutaneous infusion of ABBV-951 using the delivery system, the majority of which were non-serious and mild to moderate in severity and resolved. To address the risk of infusion site events, in addition to the routine risk minimizations measures (RMMs), AbbVie has developed and will distribute, additional RMM (aRMM) which consists of patient educational material. This will be distributed with the first dispensation of medication and upon request by the patient.

The overall aim of this study is to evaluate the effectiveness of the aRMM by estimating incidence rates of infusion site events (i.e., infusion site infections and/or serious infusion site reactions) in advanced PD patients exposed to ABBV-951 in real-world clinical practice, using data sources from Finland and France. The frequency of the infusion site events reported in the AbbVie clinical trial will be used as predefined reference values to interpret the frequency observed in this real-world study, where the aRMM will be implemented in clinical practice.

Research Question and Objectives: The following objectives will be investigated among patients with advanced PD following initiation of treatment with ABBV-951:

- To quantify the incidence rate of first infusion site event (first infusion site infection OR first serious infusion site reaction)
- To quantify the incidence rate of first infusion site infection
- To quantify the incidence rate of first serious infusion site reaction

Study Design: A longitudinal, retrospective cohort study of individuals with advanced PD treated with ABBV-951 is currently planned to be conducted in two countries: Finland and France. The overall study period will be from the date of ABBV-951's market availability (anticipated Q4 2023) until Q1 2027. Index date will be defined as the date of first initiation of ABBV-951. A censoring event will be defined as the earliest of: treatment discontinuation, end of the study period, disenrollment from the database, or death.

Population: The study population will be identified in the primary and/or secondary care data sources (depending on the results of an ongoing feasibility assessment) and will include patients aged 18 years old or more with PD treated with ABBV-951. The patient identification period will be from the date of ABBV-951's market availability (anticipated Q4 2023) to Q1 2026.

Variables: Exposure will be identified based on the first initiation of ABBV-951 (prescriptions, administration, or dispensation depending on how the drug is collected in the data sources). Outcomes will be defined based on diagnosis codes of infusion site infections and/or serious infusion site reactions within the primary care and/or secondary care data sources, wherever appropriate. Other variables of interest include demographics (directly retrieved from the data sources) and clinical characteristics (based on diagnosis codes and treatment codes).

Data Sources: The study will be conducted in two different countries, with a current preference in Finland and France based on the advances in the reimbursement, and ultimately, launch status. In order to ensure the suitability of the data sources in Finland and France to address the study objectives, a feasibility assessment is being conducted. Final decisions on databases will be made based upon launch status and feasibility assessment results.
Study Size: All patients who meet the study inclusion criteria over the patient identification period (from the date of ABBV-951's market availability to Q1 2026) within the data sources to be selected will be included. It is estimated that if a first event incidence rate of 55 per 100 person-years and 5283 person-years of exposure are observed, then the margin of error for the 95% confidence interval will be 2 per 100 persons-years for the observed rate.
Data Analysis: The incidence rate of the first outcome following first initiation of ABBV-951 will be calculated by examining the total number of first events diagnosed during the time exposed to ABBV-951 divided by the person-time contributed from index date to the first outcome or censoring (if no outcome occurs) and expressed as 100 person-years. A censoring event will be defined as the earliest of: treatment discontinuation, end of the study period, disenrollment from the database, or death. If feasible, incidence rates will be summarized by baseline characteristics i) diabetes status and ii) immunosuppression as these underlying conditions will make patients more prone to infections.
Milestones: ABBV-951 market availability: Anticipated Q4 2023; Start of data collection for secondary data use (date when data extraction starts): Est. Q1 2024; End of data collection for secondary data use (date when analytical data set is available): Est. Q1 2027; Registration in the EU PAS register: 30-day post protocol approval; Final Report of Study Results: Estimated Q1 2028.

5.0 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1		-	-	-
2		-	-	-
...		-	-	-

6.0 Milestones

Major study milestones and their planned dates are as follows:

ABBV-951 market availability	Anticipated Q4 2023
Start of data collection for secondary data use (date when data extraction starts)[a]	Estimated Q1 2024
End of data collection for secondary data use (date when analytical data set is available)	Estimated Q1 2027
Registration in the EU PAS register	30-day post protocol approval
Final Report of Study Results:	Estimated Q1 2028

a. Account for a 1-year average lag-time for access to data, data collection will start from one year after the date of distribution of Additional Risk Minimization Measures. This will depend on the characteristics of the selected databases which are under feasibility assessment.

The study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) European Union electronic Register of Post-Authorization Studies (EU PAS Register) (http://www.encepp.eu/encepp_studies/indexRegister.shtml), within 30 calendar days after the study protocol is finalized and approved by the regulatory agency. The study protocol will be disclosed to the EU PAS Register within a target of 14 calendar days following the end of data collection. The study findings will be disclosed within 30 business days after the final study report is completed and shared with the regulatory agency.

7.0 Rationale and Background

Parkinson's disease (PD) is a progressive disorder of the nervous system that results in tremors, difficulties with movement, and may eventually include morbidities related to eating or swallowing, sleep, and cognition. Globally, 6.1 million persons had PD in 2016, with approximately 38,233 people in Western Europe, 12,866 in Eastern Europe, and 9,061 in Central Europe.[1] The incidence of PD increases with age; a systematic review and meta-analysis of 21 observational studies showed that the incidence of PD is 41 per 100,000 person-years among 40 to 49 years old and increase to 1,903 per 100,000 person-years among individuals older than age 80 years.[2] PD may arise from a complex interaction of both genetic and environmental factors affecting numerous cellular processes.[3]

As PD progresses, symptoms become more severe. There is no consensus among movement disorder specialists regarding the definition of advanced PD. However, one general characteristic neurologists have agreed upon is increasing disease duration is associated with progressed PD symptoms.[4,5] European population-based studies have reported the proportion of the PD population with a disease duration of 10 or more years ranges from 19% to 37%.[6] Furthermore, first-line treatments including oral medications become less effective in advanced PD patients.[7] Algorithms based upon clinical factors and drug utilization have found the proportion of patients with PD uncontrolled on oral medications, another potential definition of advanced PD, to range from 11% to 20% of individuals with PD.[8-11] First-line treatment options for management of PD symptoms include a variety of oral medications (levodopa, dopamine agonist, monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyl transferase (COMT) inhibitors). As the disease progresses to more advanced stages, many patients become unable to manage their symptoms effectively with available oral medications.[7] Treatment options for patients with advanced PD include subcutaneous apomorphine, neurosurgery for implantation of deep brain stimulation electrodes, or placement of a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) tube for intrajejunal delivery of levodopa-carbidopa intestinal gel (LCIG).[12]

AbbVie has developed ABBV-951, which provides a 24-hour, continuous subcutaneous delivery of a 1:20 mixture (by mass) of foscarbidopa (CDP4' 12 mg/mL) and foslevodopa (LDP4' 240 mg/mL) via an ambulatory infusion pump. It is indicated for the treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of oral PD medications no longer provide adequate symptom relief. In the clinical trial, ABBV-951 was generally safe and well tolerated. Infusion site events, including infusion site reactions and infusion site infections, were observed as the drug is delivered subcutaneously using the delivery system, the majority of which were nonserious and mild to moderate in severity and were ultimately resolved. Systemic safety profile of ABBV-951 was generally consistent with the well-established safety profile of levodopa/carbidopa medications. Out of the 244 subjects exposed to ABBV-951 in Study M15-741 or its extension Study M15-737, 87 subjects (35.7%) reported an event of infusion site infection. The most commonly reported events (preferred terms [PTs]) in ≥ 5% of subjects were infusion site cellulitis, infusion site abscess, and infusion site infection. In the majority of the subjects with infusion site infections, the events were non-serious (68 out of 87), mild or moderate in severity (71 out of 87) and resolved. Some events required treatment with antibiotics and/or incision and drainage. Out of 244 subjects, 199 (81.6%) subjects experienced infusion site reactions (e.g., swelling, pain, nodule, induration, hemorrhage specific to infusion site). Serious infusion site reactions were reported in 3 (1.2%) subjects (Note: all above information taken from the EU Risk Management Plan for ABBV-951).

To address the risk of infusion site events, routine risk minimization measures (RMMs) are described in the summary of product characteristics (SmPC) such as following aseptic techniques and to frequently rotate the infusion site while using ABBV-951. In addition, AbbVie has also developed additional risk minimization measure (aRMM) which is patient educational material (patient guide) to address the risk of infusion site events. This will be distributed with the first dispensation of medication and subsequently upon request by patient as part of clinical practice to mitigate the risk of infusion site events. More specifically, these education materials will enhance patient awareness of the risks of infusion site events, provide guidance on choosing an optimal infusion site, increase

recognition and prevention of infections and reactions, and advise what to do if an infection or reaction develops. Depending on local legislation, the patient guide will be distributed to patients via patient support programs and/or healthcare personnel or other methods as agreed with local regulatory authorities.

The overall aim of this study is to evaluate the effectiveness of the aRMM by estimating the incidence rates of infusion site events (infusion site infections and/or serious infusion site reactions) in advanced PD patients exposed to ABBV-951 in real-world clinical practice, using data sources from Finland and France. In our retrospective study, the safety outcome indicators (i.e., frequency of infusion site events) cannot be compared before and after the aRMM implementation in a pre/post study design, as the patient guide will be provided at the time of ABBV-951's first initiation. When a pre/post study design is not feasible, the alternative approach suggested by EMA to assess the effectiveness of aRMM the frequency indicators in our study will be compared against a predefined reference value.[13] The predefined reference value chosen in this study is the frequency of infusion site events found in the ABBV-951 clinical trials. This will be used to discuss the frequency observed in this real-world study (where the aRMM will be implemented in clinical practice) in context with the frequency found in the clinical trial setting where the aRMM was not in place. The rationale supporting the choice of this predefined reference value is to contextualize the incidence rates in the real-world. AbbVie acknowledges that the clinical trial and real-world populations may not be as comparable (e.g., representativeness of some populations [elderly, patients with comorbidities]), therefore no formal comparisons will be performed. General considerations on this approach have been described in Section 9.10.1.

Please note that a concurrent feasibility assessment is ongoing which aims to assess the data source's suitability for evaluating the objectives as well as the variables of interest, and ultimately, the feasibility of the study in the selected data sources.

8.0 Research Question and Objectives

The overall aim of this study is to evaluate the effectiveness of aRMM by estimating the incidence rates of first infusion site events (first infusion site infections or first serious infusion site reaction) as well as first infusion site infection, and first serious infusion site reaction, in real-world clinical practice, using data sources from Finland and France. The following objectives will be investigated among patients with advanced PD following initiation of treatment with ABBV-951:

- To quantify the incidence rate of first infusion site event (first infusion site infection OR first serious infusion site reaction)
- To quantify the incidence rate of first infusion site infection
- To quantify the incidence rate of first serious infusion site reaction

9.0 Research Methods

9.1 Study Design

A longitudinal, retrospective cohort study of individuals with advanced PD treated with ABBV-951 is currently planned to be conducted in two countries utilizing primary and secondary care data sources. The overall study period will be from the date of ABBV-951's market availability (anticipated Q4 2023) until Q1 2027.

9.2 Setting

This study will be conducted in two countries where ABBV-951 will be marketed. Data sources from Finland and France are currently planned to be used. The final inclusion of both countries and data sources will be dependent on the launch and reimbursement for ABBV-951 as well as the results of the feasibility assessment exploring the data sources' suitability. Please refer to Section 9.5 for further details on the data sources.

9.2.1 Study Time Periods

The overall study period will be from the date of ABBV-951's market availability (anticipated Q4 2023) until Q1 2027. However, the patient identification period will be from the date of ABBV-951's market availability to Q1 2026. This additional 1-year in the overall study period will allow us to follow the last patients enrolled for a period of 1-year and provide sufficient time to observe the outcomes in these patients. Individual patients will be followed-up from index date to censoring (defined in the below sections). See Figure 1 for a visual depiction of the study design and key time points (Table 1).

9.2.1.1 Index Date

Index date will be defined as the date of first initiation of ABBV-951. The first prescription/administration/dispensation of ABBV-951 will be identified (choice of prescription, administration, or dispensation will be dependent on its availability within the data sources).

9.2.2 Baseline Period

A baseline period, defined as the pre-index period, including any time from when data are available up to the index date, will be used to establish clinical characteristics, whereas a short period of up to 1-year prior to or at index date will be used to determine baseline treatments (both PD-related and non-PD-related). In case of multiple values present in the data during the baseline period for a given variable, the value closest to the index date will be used. The length of baseline will be determined based on data availability in the selected data sources. It should be noted that there may be a short gap in the length of the baseline periods within our population as the inclusion criterion only requires at least 6-month of continuous enrollment (see Section 9.3.1). Please see further details in Section 9.3.3.

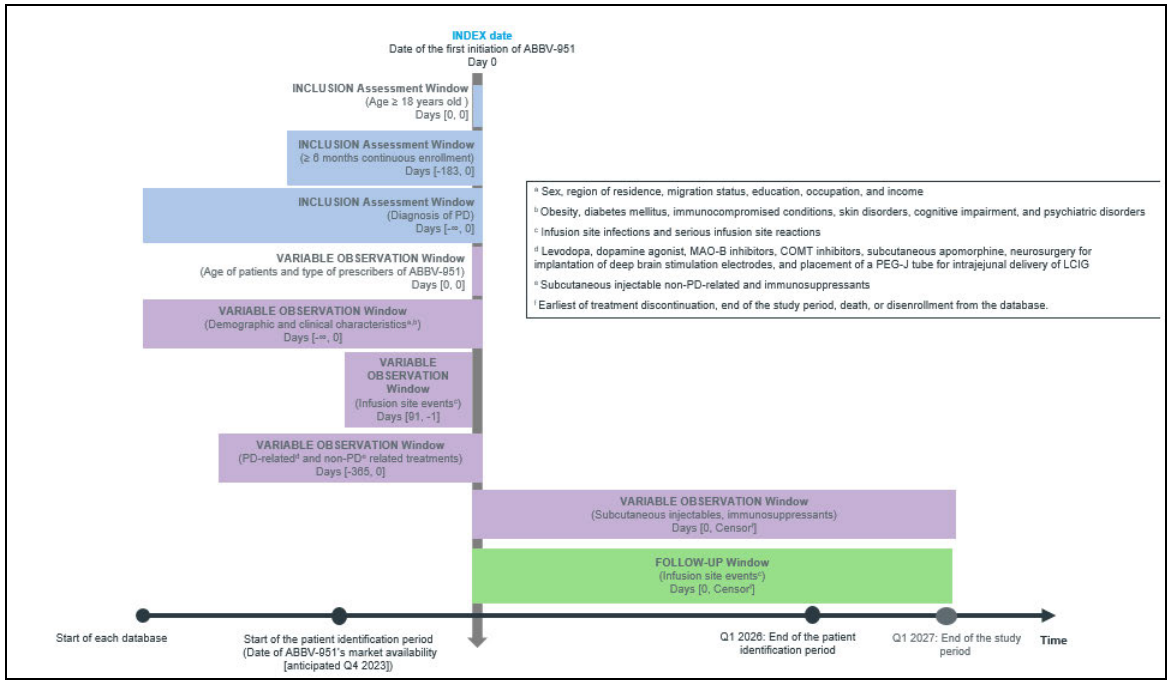
9.2.3 Follow-Up Period and Censoring

The outcomes defined as i) first infusion site event (i.e., first infusion site infection OR first serious infusion site reaction), ii) first infusion site infection, and iii) first serious

infusion site reaction will be assessed from index date (inclusive) until the earliest of treatment discontinuation, end of the study period, death, or disenrollment from the database.

Depending on data availability, treatment discontinuation will be defined as the last estimated when a prescription ends or last date of administration or dispensation of ABBV-951, with no more than a 30-day gap during follow-up. If a patient has 30 days or more gap, then the end date duration of the latest prescription or last administration or dispensation before this gap will be considered as the date of discontinuation. This definition may be refined based on data availability.

Figure 1. Study Design



COMT = Catechol-O-methyl transferase; LCIG = Levodopa-carbidopa intestinal gel; MAO-B = Monoamine oxidase-B; PD = Parkinson Disease; PEG-J = Percutaneous endoscopic gastrostomy with jejunal extension

Table 1. Time Periods

Measure	Definition
Overall study period	Date of ABBV-951's market availability (anticipated Q4 2023) to Q1 2027
Patient identification period	Date of ABBV-951's market availability (anticipated Q4 2023) to Q1 2026
Index date	Date of the first initiation of ABBV-951
Baseline period (pre-index)	Start of the database to index date (for demographic, clinical and disease characteristics) or a period of up to 1-year prior to or at index date (for treatments)
Censoring event	Treatment discontinuation, end of the study period, disenrollment from the database, or death, whichever comes first
Follow-up and analysis period	From index date to censoring event

9.3 Study Population

The study population will be identified in the primary and/or secondary care data sources (depending on the feasibility assessment results) and will include patients with PD treated with ABBV-951. Patients will be assessed for inclusion in the study population from the date of ABBV-951's market availability to Q1 2026.

9.3.1 Inclusion Criteria

Patients who meet all the following inclusion criteria will be eligible for this study:

- Patient must be ≥ 18 years old at index date
- Patients must have a diagnosis of PD (based on the available codes in the data sources which will be validated by medical experts for each country) prior to or at index date*
- Patients must have initiated ABBV-951 during the patient identification period
- Patients must have ≥ 6 months continuous enrollment (e.g., no deregistration) in the database prior to or at index date

* There is no consensus for the definition of advanced PD and PD severity level is unlikely to be captured in the data sources. Nevertheless, non-oral treatments such as ABBV-951 are indicated in advanced PD. Unless it is an off-label use, patients treated with ABBV-951 are expected to have advanced PD.

9.3.2 Exclusion Criteria

No exclusion criteria will be applied for this study.

9.3.3 Subgroups of Interest

Patients with certain clinical conditions may be more prone to infusion site infections and systemic complications from infections such as patients with diabetes mellitus and other immunocompromised conditions. Therefore, AbbVie will identify and analyze the incidence rates in the two following subgroups of interest: i) individuals with diabetes mellitus and ii) individuals with immunosuppression close to or on the date of the outcome (inclusive), if sample size and data availability allow.

The availability and how information on immunosuppressant treatment is collected will be determined in the feasibility assessment, and if feasible, an operational definition will be defined in the statistical analysis plan (SAP).

9.4 Variables

In order to meet the study objectives, the following parameters will be obtained from each data source and analyzed:

- Exposure of interest
- Demographics characteristics
- Clinical characteristics
- PD and non-PD related treatments
- Outcomes of interest

Operational definitions of these variables will be included in the SAP.

9.4.1 Exposure of Interest

Exposure will be based on drug prescriptions, administration or dispensation of ABBV-951 (depending on how the drug is collected in the data sources). In addition, type of prescriber of ABBV-951 will be reported, where available.

9.4.2 Demographic Characteristics

The following demographic characteristics will be collected during the baseline period (i.e., any time from when data are available up to the index date), where available:

- Age (collected at index date)
- Sex
- Region of residence
- Migration (e.g., emigration, immigration, country of origin)
- Education
- Occupation
- Income

In case of multiple values present in the data during the baseline period for a given variable, the value closest to the index date will be used.

9.4.3 Clinical Characteristics

The following clinical characteristics will be collected during the baseline period (i.e., any time from when data are available up to the index date), where available:

- Comorbidities:
  - Cognitive impairment
  - Psychiatric disorders
  - Obesity
  - Diabetes mellitus
  - Immunocompromised conditions such as primary (inherited condition) and secondary conditions resulting from illness, medications, or procedures (e.g., cancer, diabetes, human immunodeficiency viruses, rheumatoid arthritis, spondylarthritis, splenectomy)
  - Skin disorders (e.g., psoriasis, atopic dermatitis)
- Prior infusion site events (i.e., infusion site infections and serious infusion site reactions) within 3-month prior to index date (exclusive)

Please note this list of variables may be refined based on the data availability and specificity. Operational definitions and a full code list will be provided in the SAP.

9.4.4 Treatments at Baseline

The following treatments at baseline (e.g., a short period of up to 1-year prior to or at index date) will be reported in the study, where available:

- Oral PD-related treatments (e.g., dosage, units of measurement, where available):
  - Levodopa
  - Dopamine agonist
  - MAO-B inhibitors
  - COMT inhibitors
- Non-oral PD-related treatments (medications or surgeries)
  - Subcutaneous apomorphine
  - Neurosurgery for implantation of deep brain stimulation electrodes
  - Placement of a PEG-J tube for intrajejunal delivery of LCIG
- Subcutaneous injectable non-PD-related treatments
- Immunosuppressants treatments

Based on data availability, subcutaneous injectables (including subcutaneous apomorphine, separately) and immunosuppressant treatments will also be assessed during follow-up to perform the sensitivity and the subgroup analysis of interest, respectively (see Figure 1). If data on these treatments over follow-up are available, the operational definitions of interest will be defined in the SAP.

Please note this list of variables may be refined based on the databases availability and specificity. Operational definitions and a full code list will be provided in the SAP.

9.4.5 Outcomes of Interest

Diagnosis codes within the primary care and/or secondary care data sources will be used to identify the first infusion site event including first infusion site infection or first serious infusion site reaction. The definitions in Table 2 represent the clinical trial definitions and operational definitions of infusion site events for this real-world retrospective study. Infusion site events will be captured as diagnoses in the data sources and it will be assumed that these are events related to ABBV-951 in the study population receiving this treatment (censoring includes treatment discontinuation). In addition, sensitivity analyses will consider a potential use of other subcutaneous drugs administration during follow-up (see Section 9.8.5).

The ICD-10 CM codes for infusion site infections and serious infusion site reactions presented in Table 3 are based on medDRA preferred terms of the reported infusion site events in AbbVie clinical trial. Real-world retrospective study operational definitions for infusion site infections will be defined as: local ICD-10 diagnoses codes (for Finland and France, respectively) in the primary care visit OR outpatient visit OR inpatient hospitalization OR emergency room visit in secondary care. Real-world retrospective study operational definitions for serious infusion site reactions will be defined as: local ICD-10 diagnoses codes (for Finland and France, respectively) in the inpatient hospitalization OR emergency room visit in secondary care.

The ICD-10 CM code lists in Table 3 will be translated into the data dictionary from each country-specific data source participating in this study (e.g., local ICD-10 codes in Finland and local ICD-10 codes in France) during feasibility. It should be noted that the availability and accuracy of the codes in the local country might be limited (e.g., the codes for the skin infections and/or serious reactions may not be specific to the body part where the infusion is implemented). This will be further assessed in the feasibility assessment. Limitations on the availability and accuracy of the code lists are described in Section 9.10.2.

Table 2. Definitions of the Outcomes of Interest in Clinical Trial and in Real-World Retrospective Study

Outcomes	Clinical Trial Definitions	Real-World Retrospective Study Operational Definitions
Infusion site event (first occurrence only) defined as infusion site infection OR serious infusion site reaction	See below	See below
Infusion site infection (first occurrence only)	Infections specific to infusion site, injection site, administration site, application site, catheter site, puncture site, or medical device such as cellulitis and abscess diagnoses occurring at the target body part where infusion is implemented.	Local ICD-10 diagnoses codes (for Finland and France, respectively) in the primary care visit OR outpatient visit OR inpatient hospitalization OR emergency room visit in secondary care.
Serious infusion site reactions (first occurrence only)	Non-infection reaction/event such as redness, swelling, pain, nodule, induration, hemorrhage specific to infusion site, injection site, administration site, application site, catheter site, puncture site.	Local ICD-10 diagnoses codes (Finland and France, respectively) in the inpatient hospitalization OR emergency room visit in secondary care.

Table 3. List of ICD-10 CM Codes Identified for Infusion Site Events Based on MedDRA Preferred Terms Reported in AbbVie Clinical Trial*

ICD-10 CM codes*	
Infusion site infection	
L02.21	Cutaneous abscess of trunk
L02.41	Cutaneous abscess of limb
L02.81	Cutaneous abscess of other sites
L02.91	Cutaneous abscess, unspecified
L03.11	Cellulitis of other parts of limb
L03.31	Cellulitis of trunk
L03.818	Cellulitis of other sites
L03.90	Cellulitis, unspecified
L08.0	Pyoderma
L08.8	Other specified local infections of the skin and subcutaneous tissue
L08.9	Local infection of the skin and subcutaneous tissue, unspecified
Infusion site reaction	
R22.2	Localized swelling, mass and lump, trunk
R22.3	Localized swelling, mass and lump, upper limb
R22.4	Localized swelling, mass and lump, lower limb

* These codes will be translated to the data dictionary from each country-specific data source participating in the study.

9.5 Data Sources

The study will be conducted in two different countries, with a current preference of Finland and France based on the advances in the reimbursement, and ultimately, launch status. Table 4 describes the main characteristics of the data sources under feasibility assessment in France and Finland. This feasibility assessment is being performed to ensure the suitability of the data sources selected in Finland and France to address the study objectives. Based on the feasibility results, other countries might be proposed. Final decisions on countries and databases will be made based upon launch status and feasibility assessment results. It should be noted that data access will depend on the data release dates from each data source.

Table 4. Main Characterization of Databases Under Feasibility Assessment in Finland and France

Country	Data Sources	Data Source Type	Individuals	Database Availability	Data Dictionary (Diagnosis)	Data Dictionary (Drugs)
Finland	Prescription registers	Prescription drug register	5.5 million	1994 – Present	-	ATC
	HILMO	Secondary	5.5 million	1994 – Present	Local ICD-10	-
	AvoHILMO	Primary	5.5 million	2011 – Present	ICD-10, ICPC-2	-
	Finnish EMR	Secondary (laboratory results, clinician's notes, hospital administered drugs)	5.5 million	Each region has its own hospital district, and the start date depends on which hospital district's EMR is used	Local ICD-10	ATC
France	SNDS	Secondary (claims database)	67 million	1998– Present	Local ICD-10	ATC
	PMSI	Secondary (hospital discharge database)	67 million	1996– Present	Local ICD-10	ATC
	LPD	Primary care (EMR)	1,900,000 active patients (GP) 90,000 active patients (Neurol.)	Since 1991 – present (GP) Since 1999 – present (Neurol.)	Proprietary thesaurus (mapped to local ICD-10)	Proprietary thesaurus (mapped to ATC)

ATC = Anatomical Therapeutic Chemical; AvoHILMO = Register of Primary Health Care Visits; EMR: Electronic Medical Records; GP = general practitioner; HILMO = Care Register for Health Care; ICD = International Classification of Diseases; ICPC-2 = International Classification of Primary Care 2nd Edition; LPD = Longitudinal Patient Database; PMSI = Programme de Médicalisation des Systèmes d'Information; SNDS = Systeme National des Données de Santé.

Further details on the data sources are described in Section 9.5.1 and Section 9.5.2.

9.5.1 Finland

Linkage between the following data sources may be considered to get a comprehensive view of the patient's journey.

Prescription Registers

In Finland, there are two different prescription registers, the traditional prescription register and the new e-prescription register. The traditional prescription register is managed by the Social Insurance Institution (KELA) and has data since 1994. The e-Prescription Register (Kanta) is held by the Social Insurance Institute but managed by the National Institute for Health and Welfare (THL). Use of e-prescriptions has been compulsory in public and private health care since January 2017. The data is updated quarterly and the full data for previous year is available in March for both prescription registers. The traditional prescription register covers only reimbursed purchased medication but data on all purchased, also non-reimbursed, prescribed medication is recorded in the e-prescription register. The data contents are otherwise similar with information on e.g., the trade name, anatomical therapeutic classification (ATC) code, strength and package size of the drug product, and date of purchase. Prescription registers can be linked to other Finnish data sources.

Care Register for Health Care (HILMO; Secondary Care)

Care Register for Health Care (HILMO) is managed by the THL and has data since 1994. It contains information on secondary care (inpatient and outpatient care), e.g., type of admission, duration of hospitalization, emergency room visits, diagnoses (local ICD-10 codes) and procedures. Medical treatment is recorded at a procedure level with NOMESCO procedure codes. There is also more detailed information on the inpatient care of psychiatric patients and on procedures involving patients with advanced cardiac conditions. The quality of the data is considered mainly very high, but there is variation e.g., in the secondary diagnoses' reporting rate and accuracy. The data for the previous year is available in September. HILMO can be linked to other Finnish data sources.

Register of Primary Health Care Visits (AvoHILMO)

Register of Primary Health Care Visits (AvoHILMO) contains since 2011 data on all outpatient primary health care delivered in Finland. Since 2019, data has also been collected from the private sector and occupational health care. The register is managed by the THL and includes information on, e.g., assessment of the need for treatment, time and place of treatment, as well as diagnoses (ICPC-2 and ICD-10 codes) and procedures (SPAT and NOMESCO codes). The register also covers vaccinations given in primary health care. The validity of the data depends on the reliability and accuracy of the data reported to the register. The data is updated on a yearly basis with a lag-time similar to the HILMO register. AvoHILMO can be linked to other Finnish data sources.

Population Information System

The Population Information System has collected data on basic information on civil status, immigration/emigration data and date of death since 1969 (from 1971 in electronic format). The Population Information System includes basic information about Finnish citizens and foreign citizens residing permanently in Finland and has virtually 100% coverage.

Finnish Electronic Medical Records (EMR)

The Finnish EMRs are regional, and each hospital district has their own EMR data lakes. The hospital districts collect and release different data sets for research as they are separate entities. The main variables are available from each hospital districts EMR data lakes such as hospital administered medication, diagnoses, imaging, clinicians' notes, laboratory tests and values. EMR data lakes can be linked to other Finnish data sources.

9.5.2 France

Linkage between the following data sources may be considered.

Systeme National des Données de Santé (SNDS) is the largest and most comprehensive healthcare dataset available in Europe. It contains pseudonymized administrative and healthcare claims database, gradually developed from 1999 onwards and was converted into a useful database with the availability of individual data in 2006. The SNDS is an administrative healthcare claims database; it contains pseudonymized data of reimbursed claims for patients affiliated with one of the compulsory health insurance providers (~99% of French residents, over 66 million persons, from birth or immigration to death or emigration). This database is run by the National Health Insurance fund (Caisse Nationale d'Asssurance Maladie, CNAM).

SNDS is composed of hospital discharge summaries (PMSI), outpatients reimbursed health expenditures (données de consommation inter-régime [DCIR]) and national death registry (CépiDC database on causes of death). SNDS data consist of anonymized data of reimbursed claims for all patients affiliated with one of compulsory health insurance providers (the general scheme covers about 86% of France residents, and 14 other schemes cover the rest) and covers about 99% of French residents' population.

Data from DCIR and data from PMSI have been linked for each patient to allow for follow-up across different settings of care including outpatient practice and hospital admissions. Even if reason of death from the national death registry is not already available for all period, date of death is well recorded. Healthcare use of the patient can then be tracked for since birth/first residence in France for 10 years even if the subject is not working, changes occupation or retires and irrespective of socioeconomic status. Data from the outpatient claims database (DCIR) and from hospital discharge summaries database (PMSI) have been linked for each patient, with a pseudo-identification number as link between both parts, to make possible follow-up across different settings of care. The following information are available in the databases:

There is no loss to follow-up except for emigration.

SNDS contains information on beneficiaries age, sex, region of residence, death date (month and year), complementary universal health coverage (CMU-C) status, localization

of residence, indicator of low income and all outpatient healthcare consumption including all reimbursed prescription drugs identified by their ATC code, the date of delivery, quantity, and brand name.

Medical procedures performed on an outpatient basis or in a healthcare institution are identified by the classification commune des actes médicaux (CCAM, or common classification of medical procedures), laboratory procedures are identified by the nomenclature des actes de biologie médicale (NABM, clinical pathology test nomenclature) and paramedical or medical visits are identified by the nomenclature générale des actes professionnels (NAGP, General nomenclature of professional procedures).

SNDS informs about the presence of long-term chronic disease (LTD) status, eligible for 100% reimbursement of healthcare expenditure, the date of the LTD diagnosis, and its nature, coded according to the International Classification of Diseases (ICD-10). Registration for LTD is requested by the patient´s general practitioner, and diagnoses are approved by the health insurance medical consultant. Registration is not mandatory. It may be missing, for instance if the medical expenses are already covered by another chronic disease or the treatment is not expensive. Information on occupational diseases, sick leaves are also available.

Programme de Médicalisation des Systèmes d'Information (PMSI)

Data from PMSI includes medical summaries of all hospitalizations from all private or public hospitals, including the date of stay, medical procedures and costly innovative drugs on top of DRG (medicaments listee en sus) or implantable devices during the hospital stay, the primary diagnosis (main reason for admission), related diagnoses (species the disease context of the primary diagnosis), and diagnoses related to other comorbidities all encoded according to the ICD-10.

Longitudinal Patient Database (LPD) France

IQVIA has proprietary longitudinal patient databases (LPDs) providing systematic ongoing information from physician office-based visits on patients' consultations, diagnoses and treatment.

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in electronic medical records. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in the participating countries. Data are entered during usual patient care and submitted daily/weekly/monthly to the coordinating center, cleaned and de-identified. This data collection allows analyzing a posteriori the whole patient's prescription and care history within the database.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to three criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the general population according to age and gender distribution, as provided by national statistic authorities.

Repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills is recorded in the database. The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication.

Data from panels of primary care physicians and data from specialist panels are available. However, panels of specialists are independent of GP panel, and it is not possible to link

individual patients across the two types of practitioners. An overlap between patients included in primary health practices and in those from specialists could occur.

A probabilistic matching between the SNDS data and the EMR data can be performed based on variables common to both data sets. The variables that can be used are month of birth if available, year of birth, sex, dates of serial consultations, prescribed treatments, … These kinds of linkages are performed by the CNAM (French health insurance), the owner of the SNDS data.

9.6 Study Size

This is a descriptive drug utilization study. All initiators of ABBV-951 for the treatment of advanced PD over the patient identification period will be included. Based on data on file (not published), where an incident rate of first infusion site event of approximately 55.5 per 100 person-years with 95% of (46.4 and 64.6) is observed, AbbVie reports a range of expected values from 30 to 60 per 100 person-years in Table 5. Table 5 shows the number of person-years exposure needed to provide the stated margin of error for the 95% CI (columns) for a given incidence rate (rows). For example, if the first event incidence rate is 55 per 100 person-years and 5283 person-years of exposure are observed, then the margin of error for the 95% CI would be 2 per 100 person-years for the observed rate. The estimation of sample size in Table 5 is done assuming that infusion site events follow a Poisson distribution.[14]

Table 5. Number of Person-Years Exposure Needed for a Given Incidence Rate (IR) of Infusion Site Infections and Desired Margin of Error for the 95% CI

	Margin of Error for the 95% CI				
First Infusion Site Infection IR	**1 per 100 person-yrs**	**2 per 100 person-yrs**	**3 per 100 person-yrs**	**4 per 100 person-yrs**	**5 per 100 person-yrs**
30 per 100 person-yrs	11525	2882	1281	721	461
35 per 100 person-yrs	13446	3362	1494	841	538
40 per 100 person-yrs	15366	3842	1708	961	615
45 per 100 person-yrs	17287	4322	1921	1081	692
50 per 100 person-yrs	19208	4802	2135	1201	769
55 per 100 person-yrs	21129	5283	2348	1321	846
60 per 100 person-yrs	23049	5763	2561	1441	922

9.7 Data Management

This study will follow the relevant ENCePP Guide on Methodological Standards in Pharmacoepidemiology and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for data management.

Data management for this study will be conducted using standard IQVIA processes. Further details on the data handling procedures will be provided in the SAP or data management plan. IQVIA will adhere to all local and regional laws on data protection and privacy.

9.8 Data Analysis

9.8.1 General Considerations

Upon first initiation of ABBV-951, patient characteristics including demographics, baseline clinical characteristics and baseline treatment variables will be assessed based on data availability. Please refer to Section 9.4.2, Section 9.4.3, and Section 9.4.4 for details on those variables. For continuous variables, mean, standard deviation, median, 25th and

75th percentiles, minimum and maximum values (when available depending on the country) and the number of missing values will be reported. For categorical variables, the frequency, percentage, and number of missing values will be reported. No missing value imputation will be performed. The study results will be discussed in context with those observed in the AbbVie clinical trial, but without formal comparisons.

9.8.2 Analysis for Objectives

The incidence rate of first infusion site events defined as i) first infusion site infection or first serious infusion site reaction, as well as ii) first infusion site infection, and iii) first serious infusion site reaction, following first initiation of ABBV-951 will be calculated by examining the person-time contributed from index date to the first occurrence of the event or censoring (if no outcome occurs). Please refer to Section 9.4.5 for more details on the outcome's definitions. Since AbbVie is considering the occurrence of the first event only in each patient, the incidence rate can be interpreted as the number of first infusion site event over the period of exposure to ABBV-951 and expressed as 100 person-years, or the number of patients reporting at least one infusion site event per 100 person-years. The corresponding confidence interval (CI) will be presented. In addition, the proportion of patients with at least one outcome of interest will be reported.

$$\text{Incidence event rates (per 100 person-years)} = \frac{\text{Total numbers of first events diagnosed over the period of exposure to ABBV}-951}{\text{Total time at risk (in years)}} \times 100$$

9.8.3 Stratification by Subgroups of Interest

AbbVie will stratify our analyses by patients with i) diabetes status and ii) concomitant use of immunosuppressants close to or on the date of the outcome (inclusive), if sample size and data availability allow. Incidence rates of first infusion site and proportions of patients with at least one outcome of interest in each subgroup of interest will be reported as described in Section 9.8.2.

9.8.4 Combining Results Across Data Sources

If appropriate, aggregated results may be pooled across countries using suitable methods of meta-analysis to compute overall estimates. Specific details will be described in the SAP.

9.8.5 Sensitivity Analysis

A sensitivity analysis (a) excluding patients with any prior infusion site events (i.e., same outcomes definitions of infusion site infections and serious infusion site reactions) within 3 months prior to index date will be conducted in order to select patients free of events of interest at index date and avoid overestimation of events to be considered ABBV-951 related. Similarly, two other sensitivity analyses will be conducted: (b) exclusion of patients with subcutaneous treatments during follow-up and (c) exclusion of patients with subcutaneous apomorphine use during follow-up in the main study population.

9.9 Quality Control

IQVIA Quality Management System

This study will be conducted according to the International Society for Pharmacoepidemiology's 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' (42) and 'Guideline on good pharmacovigilance practices (GVP), Module VIII – Post-authorisation safety studies (Rev 3)', 09 October 2017 (EMA/813938/2011 Rev 3).

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work frame of IQVIA Quality Management System and in accordance to the following manual, operating procedures and work instructions:

- RWI_MAN_RWW0007 Real-World Quality Manual
- RWI_OP_PM0004 Real World Project Quality Control
- RWI_OP_PM0020 Real-World Records Management
- RWI_OP_PM0003 Post-Authorisation Safety Studies (PASS)
- RWI_WI_EPI0005 Protocol Development

- RWI_WI_EPI0004 Quality Control of Biostatistics and Epidemiology Deliverables

According to the policies and procedures above, a study-specific Quality Control plan will be developed and executed, which will include quality control on the protocol in general, the study methodology, the SAP, programming, data management and analysis, and study report.

Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.
- IQVIA project management will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team. Also, the project management will ensure that IQVIA employees assigned to the project are trained on protocol and project-specific procedures, as per IQVIA procedure RWI_WI_PM0035 "Real-World Project Specific Training and Staff Transition."

9.10 Limitations of the Research Methods

9.10.1 General Considerations

Our results from this real-world study will be interpreted in context with the results from AbbVie clinical trial but without formal comparisons, as mentioned in Section 7.0 and Section 9.8.1. Key baseline demographic and clinical characteristics, that may explain the

potential differences in the outcomes' frequency observed in the clinical trial versus the real-world study, will be investigated and considered in subgroup analysis, conditional on data availability. For example, the proportion of patients with diabetes or concomitant use of immunosuppressants (known risk factors for infections and systemic complications from infections) will be described in this real-world study and analyses will be stratified by these two conditions. This retrospective study cannot ascertain process indicators, such as whether risk minimization materials (i.e., patient guide) were in fact delivered by the healthcare professionals or received and used by the patients.[13] Therefore, any considerations regarding the effectiveness of the aRMM will be limited by the assumption that these were successfully implemented in clinical practice. In addition, as with any observational secondary database study, there might be potential limitations in conducting the study following the proposed study design and using the proposed data sources. Electronic patient healthcare data are collected primarily for the management, billing and/or reimbursement of patient care and not for research purposes. Hence, the utility of findings from research leveraging electronic healthcare data is limited by the completeness and accuracy of coding for these variables and proxy variables in the data sources to be utilized.

9.10.2 Information Bias

There is no consensus for the definition of advanced PD, and severity level is unlikely to be captured in the data sources. Nevertheless, non-oral treatments such as ABBV-951 are indicated in advanced PD. Patients treated with ABBV-951 are assumed to be advanced PD, as per the label. As non-oral treatments are constringent for the patients due to the route of administration, our assumption is that these prescriptions will be only made when oral medications are less effective and hence in concordance with the indication ('treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of oral PD medications no longer provide adequate symptom relief').

Furthermore, the outcomes of interest would be infusion site events related to ABBV-951's administration. However, infusion site events will be captured as diagnoses

in the primary and/or secondary data sources and only assumed to be related to ABBV-951 in the study population that will be receiving this treatment (censoring includes treatment discontinuation), leading to potential outcomes' misclassification. Additionally, events on specific infusion sites might not be determined directly from data sources included in this study and the local codes might not be granular enough to provide such information. Therefore, our study may include generalized skin infections or reactions, occurring at any site and not necessarily at the infusion site after initiation of ABBV-951, leading to potential outcomes' misclassification and overestimation. The quality and accuracy of coding will be investigated in the feasibility assessment and any discrepancies will be reported. Similarly, patients may be susceptible for the events of interest when using other subcutaneous administration such as apomorphine, leading to potential outcomes' misclassification and overestimation. Hence, AbbVie will perform a sensitivity analysis excluding patients with any subcutaneous injectables or apomorphine use during the follow-up. This will provide information on to which extent ABBV-951 alone can lead to those events during the follow-up, and whether AbbVie may overestimate the incidence rates.

Lastly, a pre-index period including any time from when data are available up to the index date will be used to assess the baseline clinical characteristics. During the feasibility assessment, the impact of enrollment duration period prior index date on the baseline data completeness will be assessed. If the feasibility results suggest that the enrollment period could introduce information bias (i.e., patients with a longer enrollment period have more comorbidities recorded than patients with a short enrollment period), then AbbVie may restrict the period for assessing baseline clinical characteristics to 1-year.

9.10.3 Generalizability

The data sources from Finland and France will be representative of study population in the respective countries and therefore the likelihood of selection bias is minimal. In Finland, all Finish residents have a personal identification number which is used to record all medical information (i.e., clinical diagnosis, prescriptions, procedures…) in the selected databases (see Section 9.5.1). Similarly, SNDS and PMSI cover ~99% of the

French's residents. It should be noted that LPD France only includes a panel of physicians. However, this panel is a representative sample of primary care physician population according to age, sex, and geographical distribution. Additionally, the population in the data source is representative of the general population according to age and gender distribution in France (see Section 9.5.2). In addition, in real clinical practice, patients might experience the outcome of interest multiple times. However, this study aims to investigate only the first occurrence of the outcome during the follow-up and will not provide estimates of the number of recurring events per patient.

9.11 Other Aspects

To preserve patient confidentiality at the reporting stage, data will be released at a high enough level of aggregation to prevent readers being able to 'recognize' a particular individual. Values from 1 to 5 will be masked according to the data protection requirements and a special character such as ¥ will be substituted to indicate a suppressed value. Where only a single count within a category has been suppressed and therefore could be further identified, both this result and the next lowest number will be suppressed to avoid calculation of the small value.

10.0 Protection of Human Subjects

As a non-interventional study using de-identified secondary data, this study does not pose any risk to patients. The study will be conducted in accordance with all legal and regulatory requirements. The European Union (EU) registries receive ethical approvals as required by applicable laws and regulations in their respective country. Additionally, AbbVie will adhere to commonly accepted research practices, including those described in the following guidance documents: ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, and FDA Guidance for Industry and FDA Staff: Best Practices for

Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.[15-18]

11.0 Plans for Disseminating and Communicating Study Results

One comprehensive study report will be produced at the conclusion of the study. This report will be submitted to the appropriate regulatory authorities. The report will include a presentation of the registry design, methodology, and results of the biostatistical analysis.

AbbVie may also consider reporting the study data at scientific conferences or in scientific journals. Preparation of such manuscripts will be prepared in accordance with the current reporting guidelines for observational routinely collected health data statement for pharmacoepidemiology.[19-21]

12.0 Management and Reporting of Complaints (Safety and Quality)

This is a non-interventional study based on data previously collected under routine clinical care; therefore, AEs reporting at the individual case level will not be required. Good pharmacovigilance practices (GVP), Module VI Section VI.C.1.2.1.2 guidance will be followed on reporting of AEs in non-interventional post-authorization studies with a design based on secondary use of data.[22]

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Annex 1. List of Stand-Alone Documents

Not applicable.

Annex 2. ENCePP Checklist for Protocols

Doc. Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)
Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked, and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the GVP.

Study title: A Retrospective Cohort Study Estimating Incidence Rates of Infusion Site Events with ABBV-951 for the Treatment of advanced Parkinson's Disease.

EU PAS Register® number: To be registered
Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	6.0
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

This will be registered 30-day post protocol approval.

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	7.0 and 8.0
2.1.3 The target population? (i.e., population or sub-group to whom the study results are intended to be generalized)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a descriptive study, and the results will be interpreted against the results from the

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

2 Date from which the analytical dataset is completely available.

clinical trials considering the limitations associated with this approach.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.8.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Only secondary care data sources will be used for the study (i.e., no primary data collection).

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☐	☒	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	9.2 and 9.4
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.3

Comments:

Data sources are not yet confirmed. The choice will be made according to the suitability of those data sources for our study objectives in the feasibility assessment.

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.4.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorized according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

ABBV-951 will be defined as the exposure. How this is captured will be based on feasibility results.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.4.5
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.4.5
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.4.5 and 9.10.1
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

The outcomes will be based on diagnoses codes and on the assumption that these will be related to the continuous use of ABBV-951 (censoring includes ABBV-951 discontinuation). It should be noted that the diagnoses codes may lack granularity to specifically identify the outcomes. This will be assessed in the feasibility assessment and decision will be made on the validity of those diagnoses' codes for the outcomes of interest.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10.1

Comments:

This is a descriptive study, and the results will be interpreted against the results from the clinical trials considering the limitations associated with this approach.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

This is a descriptive study, and the results will be interpreted against the results from the clinical trials considering the limitations associated with this approach.

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☒	☐	

Section 9: Data sources	Yes	No	N/A	Section Number
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☒	☐	
9.1.3 Covariates and other characteristics?	☐	☒	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.1-9.44
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4.5
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.5

Comments:

ABBV-951 is not yet on the market and there is no recommendation yet on whether this should be dispensed at hospital or community pharmacy. Therefore, in the feasibility assessment will assess the data's suitability for this study in terms of availability and accuracy of the exposure (by using a proxy at hospital or community pharmacy), and the outcomes of interest. It should be noted that in the current protocol, ICD-10 CM codes for the outcomes are listed, but those will be translated into the local data dictionary.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	

Comments:

Outcome operational definitions will depend on the accuracy of the data dictionary, the use of the codes in the databases, and real-world clinical practice.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	9.10

Section 12: Limitations	Yes	No	N/A	Section Number
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.6

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.0

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.0

Comments:
