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Protocol for Study M15-741

Parkinson's Disease: Safety and Tolerability of 24-Hour Daily Exposure to ABBV-951 by Continuous Subcutaneous Infusion

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ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-951	EUDRACT:	2018-002144-85

FULL TITLE: A 52-Week, open-label, single-arm study to evaluate the safety and tolerability of 24-hour daily exposure of continuous subcutaneous infusion of ABBV-951 in subjects with Parkinson's disease

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1 SYNOPSIS

Title: A 52-Week, open-label, single-arm study to evaluate the safety and tolerability of 24-hour daily exposure of continuous subcutaneous infusion of ABBV-951 in subjects with Parkinson's disease	
Background and Rationale:	ABBV-951 (carbidopa phosphate/levodopa phosphate [CDP/LDP]) is a soluble formulation of carbidopa (CD) and levodopa (LD) prodrugs that is deliverable by continuous subcutaneous infusion (CSCI). ABBV-951 undergoes enzymatic conversion to CD/LD and has the potential to achieve efficacy similar to that of levodopa-carbidopa intestinal gel (LCIG, denominated as carbidopa-levodopa enteral suspension [CLES] in the United States) by subcutaneous delivery. This study is conducted to assess the safety and tolerability of the long-term use of ABBV-951 in Parkinson's disease patients, whose motor symptoms are inadequately controlled by their current treatment.
Objectives and Endpoints:	Primary Objective: • To assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for up to 52 weeks Secondary Objective: • To assess the efficacy of ABBV-951 as measured by patient-reported and rater-measured efficacy endpoints Primary Endpoints: • Percentage of subjects with adverse events (AEs) and serious adverse events during the study • Percentage of subjects with AEs of special interest (AESIs) during the study • Percentage of subjects with numeric grade equal to or higher than 5 and percentage of subjects with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study • Change in clinical laboratory test data from Baseline to end of study • Change in vital sign measurements from Baseline to end of study • Change in electrocardiograms from Baseline to end of study Secondary Endpoints are change from Baseline to end of study for the following: • Average normalized daily "Off" time and "On" times as assessed by the PD Diary • PD symptoms as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I-IV (or the UPDRS I-V in countries where a validated translation of the MDS-UPDRS is not available) • Sleep symptoms as assessed by the PD Sleep Scale-2 (PDSS-2) • Quality of life as assessed by the PD Questionnaire-39 items (PDQ-39) • Health-related quality of life as assessed by the EuroQol 5-dimensions questionnaire (EQ-5D-5L) Exploratory Endpoint: • PD symptoms (including tremor, bradykinesia, dyskinesia, daytime

	somnolence, and indication of propensity for impulsive behaviors) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device (as allowed by local regulations) from Baseline to the Week 26 Visit
Investigators:	Multicenter
Study Sites:	Approximately 65 sites globally
Study Population and Number of Subjects to be Enrolled:	Approximately 240 adult subjects with PD whose motor symptoms are inadequately controlled by oral medications.
Investigational Plan:	Phase 3, open-label, single-arm study in an outpatient setting
Key Eligibility Criteria:	• Adult male or female subjects, 30 years of age or older at the time of screening, with a diagnosis of idiopathic PD that is levodopa-responsive • Subjects must be judged by the investigator to be inadequately controlled by current therapy, have a recognizable/identifiable "Off" and "On" states (motor fluctuations), and have a minimum of 2.5 hours of "Off" time per day
Study Drug and Duration of Treatment:	ABBV-951 CSCI for 24 hours daily for 52 weeks
Date of Protocol Synopsis:	11 February 2021

2 INTRODUCTION

2.1 Background and Rationale

Why This Study is Being Conducted

ABBV-951 (carbidopa phosphate/levodopa phosphate [CDP/LDP]) is a soluble formulation of carbidopa/levodopa (CD/LD) prodrugs that is deliverable by continuous subcutaneous infusion (CSCI). ABBV-951 undergoes enzymatic conversion to CD/LD and has the potential to achieve efficacy similar to levodopa-carbidopa intestinal gel (LCIG, denominated carbidopa-levodopa enteral suspension [CLES] in the United States [US]) by subcutaneous delivery.

Patients with Parkinson's disease (PD) require a therapeutic approach that is tailored to their unique needs and responses to levodopa. ABBV-951 enables continuous, subcutaneous, and individualized delivery of CD/LD, covering the wide range of levodopa doses required to adequately control motor symptoms in patients with advanced PD (aPD). Therefore, this novel treatment may provide an alternative therapy to many patients whose motor complications are inadequately controlled by their current treatment.

While the systemic toxicology and tolerability profiles of CD/LD are well established preclinically and in humans, the local (skin) and systemic tolerability following subcutaneous delivery of ABBV-951 are less known and are being assessed within the scope of this study.

Systemic and local tolerability have been measured in animal models, as well as in the clinical setting. In Good Laboratory Practice (GLP)-compliant preclinical studies in rats and monkeys, doses of ABBV-951, considered therapeutically relevant in PD patients, were demonstrated to be well tolerated at the infusion site and did not significantly increase serum phosphate levels. Local irritation was assessed in dogs at a 50/200 mg/mL concentration, following CSCI for 28 days with a fixed indwelling catheter at a rate of 0.1 or 0.25 mL/hour (120/480 mg/day and 300/1200 mg/day, respectively). 120/480 mg/day was well tolerated, and the infusion site findings were similar to those of the vehicle control without signs of irritation or inflammation stemming from ABBV-951. Findings at the infusion site of animals treated with the higher infusion rate (0.25 mL/hour) were confounded by a concurrent bacterial infection, and it was not possible to clearly determine whether ABBV-951 was well tolerated; however, the infusion of ABBV-951 at the same concentration (50/200 mg/mL), but at a higher infusion rate (0.5 mL/hour) for fewer days (5 days) was well tolerated, with only minimal signs of irritation at the infusion site. In cohorts from the Phase 1 study in healthy volunteers (Study M15-733), in which ABBV-951 was administered as a loading dose followed by a continuous infusion for up to 72 hours, levodopa exposure showed a low degree of fluctuation, similar to what was observed with the LCIG registration studies. ABBV-951 was generally well tolerated, with only mild reports of pain at the infusion site related to high flow rates used to deliver loading doses. These reports of infusion site pain were significantly reduced when the flow rate was adjusted to deliver the loading dose over a longer period of time. No other local tolerability issues were observed, and no subject discontinued the study due to these events. No pain or other safety or tolerability interim issues have been reported from ongoing Phase 1 studies in PD patients, where ABBV-951 is administered at therapeutic doses for 24 or 72 hours (Study M15-738) or for up to 28 days (Study M15-739).

The dose ranges of ABBV-951 to be utilized in this study are similar to those administered in the Phase 1 studies in PD subjects (Studies M15-738 and M15-739); however, the duration of the continuous infusion administration will be long-term. Therefore, subject safety and tolerability over long-term exposure will need to be assessed.

This open-label, single-arm, Phase 3 study will be conducted in an outpatient setting to evaluate local and systemic safety and tolerability, and explore the efficacy of therapeutic doses of ABBV-951 infused continuously for 52 weeks in subjects with PD.

Clinical Hypothesis

CSCI of ABBV-951 is safe and well-tolerated for up to 52 weeks in PD patients with motor fluctuations no longer controlled by current PD medications.

2.2 Benefits and Risks to Subjects

The combination of oral levodopa and DOPA decarboxylase inhibitors (DDCI), such as carbidopa or benserazide, has been used for many years in patients with PD to control motor symptoms, and the systemic safety profile is well established. Furthermore, achieving stable plasma levodopa concentrations through continuous infusion has been demonstrated previously with LCIG and resulted in greater efficacy than oral CD/LD as assessed by a reduction in overall daily "Off" time accompanied by increased "On" time without troublesome dyskinesia. Therefore, it is anticipated that ABBV-951 can provide a similar benefit if plasma levodopa concentrations can be maintained stable and within the therapeutic window.

Potential risks of receiving an ABBV-951 dose lower than required for PD symptom control include experiencing an exacerbation of PD symptoms ("Off" state) characterized by increased difficulty with movement, tremor, and stiffness. Potential risks of receiving an ABBV-951 dose higher than what is required for motor symptom control include experiencing dyskinesias (abnormal or uncontrolled movements) and hallucinations. Other anticipated risks are well characterized levodopa-related side effects, including nausea, vomiting, and dizziness; however, not all of the potential side effects of the drug are known. Subjects may also experience general discomfort or inconvenience related to study procedures.

Since ABBV-951 is administered as a CSCI, there is a potential for safety issues related to infusion site tolerability. These issues may include infusion site irritation and inflammation (swelling, redness, pain, itching), bruising, skin infection, and discomfort related to the feeling of liquid flowing through the needle/cannula. Data from preclinical studies and from a study in healthy volunteers show that infusion is generally well tolerated; however, the ABBV-951 infusion rates (i.e., flow rates) that will be used in the current study are anticipated to be higher than those used in the healthy volunteer study and therefore local tolerability at the infusion site will be a specific focus in this study.

For details, please see the safety data in the ABBV-951 investigator's brochure.[1]

Based on the limited information available to date, exposure to ABBV-951 does not appear to pose additional risks to study participants because of the coronavirus disease-2019 (COVID-19). ABBV-951 metabolizes into LD and CD, sharing the same characteristics of these compounds, which are commonly used as symptomatic treatment of PD globally.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

To assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for up to 52 weeks.

Secondary

To assess the efficacy of ABBV-951 as measured by patient-reported and rater-measured efficacy endpoints.

3.2 Primary Endpoints

1. Percentage of subjects with adverse events (AEs) and serious adverse events (SAEs) during the study
2. Percentage of subjects with AEs of special interest (AESIs) during the study
3. Percentage of subjects with numeric grade equal to or higher than 5 and percentage of subjects with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study
4. Change in clinical laboratory test data from Baseline to end of study
5. Change in vital sign measurements from Baseline to end of study
6. Change in electrocardiograms (ECGs) from Baseline to end of study

3.3 Secondary Endpoints

The efficacy endpoints are change from Baseline to end of study for the following:

1. Average normalized daily "Off" time and "On" times as assessed by the PD Diary
2. PD symptoms as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I-IV (or the UPDRS Parts I-V in countries where a validated translation of the MDS-UPDRS is not available)
3. Sleep symptoms as assessed by the PD Sleep Scale-2 (PDSS-2)
4. Quality of life as assessed by the PD Questionnaire-39 items (PDQ-39)
5. Health-related quality of life as assessed by the EuroQol 5-dimensions questionnaire (EQ-5D-5L)

3.4 Exploratory Endpoint

PD symptoms (including tremor, bradykinesia, dyskinesia, daytime somnolence, and indication of propensity for impulsive behaviors) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device (as allowed by local regulations) from Baseline to the Week 26 Visit.

3.5 Exploratory Research: Biomarker Research Endpoints

Optional samples will be collected during the study to evaluate known and/or novel biomarkers related to PD, related conditions, ABBV-951, or drugs of a similar class. Deoxyribonucleic acid (DNA) samples may be analyzed for genetic markers that may help to understand PD and the subject's response to ABBV-951. Genes of interest may include (but are not limited to) those associated with pharmacokinetics (drug metabolizing enzymes, drug transport proteins), genes within the target pathway (dopaminergic pathways), or other genes believed to be related to PD (alpha-synuclein [SNCA]). Research may also include epigenetic changes in DNA that may correlate with the subject's response to treatment or disease. Research on samples collected will follow country-specific regulations. This research is exploratory in nature, and the results may not be included within the clinical study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Design and Schematic

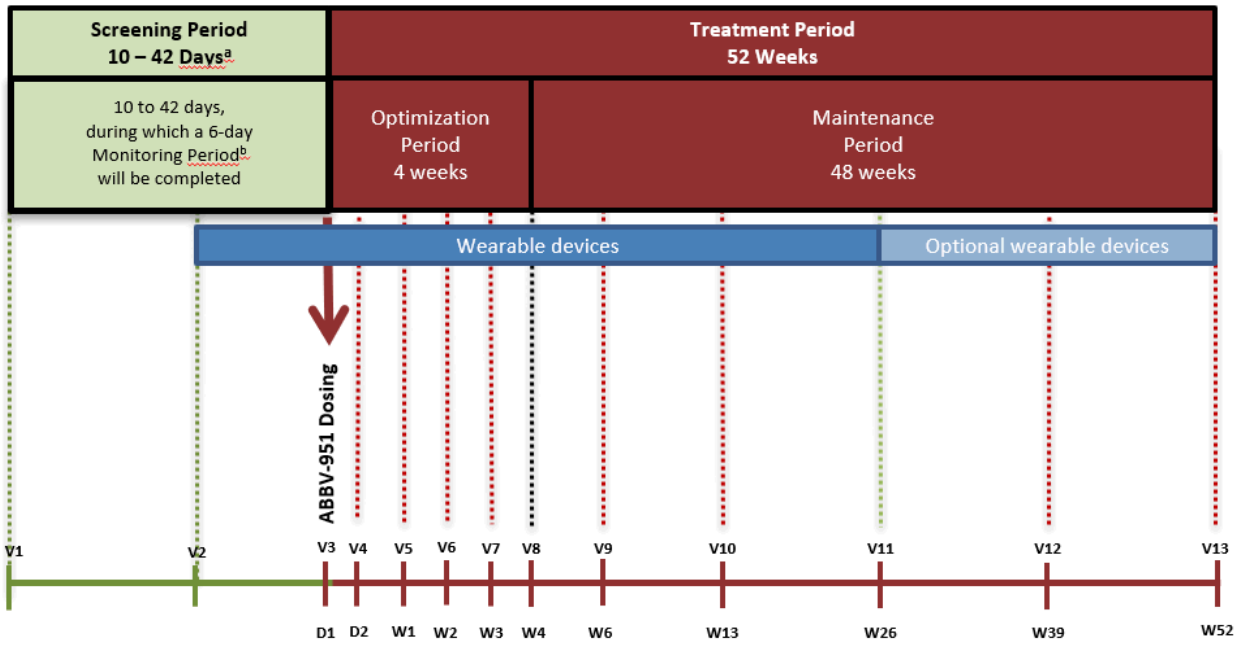
This is a 52-week, Phase 3, open-label, single-arm, multicenter study to assess the local and systemic safety and tolerability, as well as efficacy, of ABBV-951 administered as a CSCI for 24 hours daily for up to 52 weeks. At study completion, subjects may transition to a 24-hour CSCI of ABBV-951 open-label extension study. Approximately 240 adult subjects with PD whose motor symptoms are inadequately controlled despite their current optimized PD therapy will be enrolled.

Two interim analyses will be performed during the course of this study. The first interim analysis will be performed after at least 100 subjects have completed 26 Weeks of therapy; the second interim analysis will be performed after at least 100 subjects have completed 52 Weeks of therapy.

See Section 5.1 for eligibility criteria. Safety parameters, such as clinical laboratory test results, ECGs, and vital signs will be monitored throughout the study (see Sections 3.11, 3.14, and 3.15, respectively, of the Operations Manual [Appendix F]).

A schematic of the study is shown in Figure 1. Details regarding study procedures are located in Section 3 of the Operations Manual (Appendix F).

Figure 1. Study Design Schematic



D = Day; V = Visit; W = Week

a. *The Screening Period may be extended up to a total of 90 days for extenuating circumstances, e.g., supply constraints.*

b. *The Monitoring Period can occur any time before V3, as long as it lasts for 6 consecutive days. PD Diaries will also be collected for at least 2 consecutive days during the Monitoring Period. In countries where the PKG watch is not approved, the Monitoring Period may be reduced to at least 2 days to account for the collection of PD Diaries and pump training.*

Note: As allowed by local regulations, subjects will receive the PKG-watch following Screening Visit 1 (V1) and will be required to wear it (refer to the currently approved manufacturer's directions) during the Monitoring Period and at least until the completion of Week 26 (V11); thereafter, wearing of the PKG-watch will be optional. The Monitoring Period consists of at least 6 consecutive days during the Screening Period (prior to V3) where subjects will be required to collect PD diaries and wear the PKG watch at the same time. "As allowed by local regulations" is applicable to all wearable device references throughout this protocol and its appendices. The AbbVie Therapeutic Area Medical Director (TA MD) should be consulted if, in the opinion of the Investigator, there are circumstances that might interfere with the use of the PKG device (e.g., religious reasons, atopic dermatitis). A subject's inability to wear the PKG watch, due to logistics hindering the watch from being made available, will not preclude him/her from study participation.

Study Periods

Screening Period

The intended 10- to 42-day Screening Period (may be extended up to a total of 90 days for extenuating circumstances) will consist of 2 screening visits (V1 and V2) and a 6-day Monitoring Period, to be completed any time before V3. Subjects will become familiar with the wearable device and the PD Diary during the Screening Period. During the Screening Period, subjects must be on a stable oral PD medication regimen for at least 30 days prior to commencing ABBV-951. Historical data (medical records, etc.) are acceptable documentation for the use of stable medication.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 30 days prior to initial study drug administration, whichever is longer, with the exception of medications containing levodopa and catechol-*O*-methyltransferase (COMT) inhibitors, which must be discontinued for at least 12 hours before initiation of study drug and for the duration of the Treatment Period. The Screening Period may be extended up to a total of 90 days for extenuating circumstances, e.g., supply constraints.

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility. See Section 5.3. The investigator or his/her designee must confirm continued subject eligibility at V3, prior to enrollment. Considering historical data and the minimum time required for the Monitoring Period, the Screening Period may be completed in as short as 10 days; it should be targeted to be completed in approximately 40 days and should not exceed a total of 90 days overall.

Subjects will be required to wear the wearable device for 6 consecutive days prior to Visit 3 (i.e., the 6-Day Monitoring Period), in countries where such devices are approved. The PD Diaries should be completed for at least 2 consecutive days of the 6-day Monitoring Period, prior to Visit 3 (Day 1).

Treatment Period

The Treatment Period starts with the initiation of ABBV-951 and consists of 2 parts: a 4-week Optimization Period and a 48-week Maintenance Period.

Optimization Period: during the 4 weeks of the Optimization Period, investigators will make all necessary adjustments to the subject's ABBV-951 dose until the optimal clinical response for the individual subject is obtained. Additional adjustments may be required for the subject's concomitant PD medications (e.g., dopamine-agonists, selective monoamine oxidase B [MAO-B] inhibitors, amantadine, safinamide), including tapering down or even suspending such medications, in accordance with the prescribing information, to achieve the therapeutic approach that, in the investigator's opinion, controls the subject's symptoms in the most satisfactory way.

Maintenance Period: the Maintenance Period will consist of 48 weeks of a 24-hour daily CSCI of ABBV-951 at the optimal therapeutic dose. During this 48-week period, subjects should maintain a stable regimen of all concomitant medications unless changes are considered medically necessary, in the opinion of the investigator. ABBV-951 can be adjusted throughout the study. In the event of dose adjustments for ABBV-951 or other concomitant medications (including adding or suspending other PD medications) these adjustments should be documented in the electronic case report form (eCRF).

On the morning of Day 1 (V3) subjects will need to be in a clinically defined "Off" state (i.e., no PD medications for at least 12 hours before initiation of study drug). After confirmation of eligibility and a brief clinical examination, subjects will receive an oral loading dose of LD+DDCI followed by the beginning of the subcutaneous infusion of ABBV-951 at their calculated starting dose.

For each subject, the starting dose level for the continuous infusion rate of ABBV-951 will be calculated according to their baseline dose of oral levodopa (or levodopa equivalent dose [LED]), based on the proposed conversion rates from Tomlinson et al,[2] guidance from Espay et al,[3] and a conversion algorithm based on data from Phase 1 studies (see Section 4.2).

Subjects might also resume PD medications that do not contain levodopa or COMT inhibitors (such as dopamine agonists, MAO-B inhibitors, amantadine, safinamide, etc.) as these concomitant medications

are not required to be suspended before starting ABBV-951. However, per the investigator's judgment and according to the prescribing information, subjects may start to taper off concomitant PD medications during the 4 weeks of the Optimization Period.

Subjects will be evaluated on the day of, and the day after, initiating ABBV-951, and then weekly during the Optimization Period. During each visit, the investigator will assess the subject's PD symptoms by interview and neurologic examination and may adjust the subject's therapeutic regimen by continuing tapering off and/or suspending previous concomitant PD medications, and at the same time increasing, decreasing, or maintaining the ABBV-951 infusion rate based on the subject's clinical response. If all concomitant PD medications have been tapered off, the dose of ABBV-951 may be further adjusted until the optimal clinical response for the individual subject is obtained, as determined by the investigator. Optimal clinical response is defined by maximizing the functional "On" time and minimizing the number of "Off" episodes during the day. This optimization also minimizes "On" time with troublesome dyskinesia.

During the Optimization Period, study visits will occur as follows:
Day 1 (V3)
Day 2 (V4)
Week 1 (V5)
Week 2 (V6)
Week 3 (V7)
Week 4 (V8)

The investigator may perform unscheduled visits to make any needed adjustments within the 4-week Optimization Period.

After Week 4 (V8), all subjects will begin the Maintenance Period and should maintain a stable treatment regimen of ABBV-951 and other concomitant medications, including any PD medications that are still being administered after the Optimization Period. Dose adjustments of medications, including ABBV-951, can be made if considered medically necessary, in the opinion of the investigator. Any changes to medications or the dose of ABBV-951 should be recorded in the eCRF.

During the Maintenance Period, study visits will occur as follows:
Week 6 (V9)
Week 13 (V10)
Week 26 (V11)
Week 39 (V12)
Week 52 (V13) or in case of premature discontinuation.

All visits, apart from the Screening visits (V1 and V2) and V3 (Day 1), will be allowed a window of ± 3 days.

As part of the study procedures, study drug is intended to be dispensed to subjects every 2 weeks during the Treatment Period with or without a clinic visit being completed.

Unscheduled clinic visits may occur per investigator discretion as deemed necessary. The appropriate protocol assessments to be conducted at an unscheduled clinic visit are to be determined by the

investigator. Additionally, a subject (or authorized representatives, if allowed per local regulations) may return to the clinic site for additional study drug or drug delivery system components or accessories.

In rare situations where a visit cannot be completed onsite due to an extenuating event (e.g., COVID-19-related conditions), some assessments may be performed remotely. Refer to the Operations Manual (Appendix F) for further guidance.

Treatment Arm

Subjects will receive an oral loading dose on Day 1 (V3) followed by a 24-hour daily subcutaneous infusion of ABBV-951. The loading dose will be established by the investigator per the subject's oral regimen prior to commencing ABBV-951 (see Section 4.2). The starting continuous infusion rate (F1) will be calculated taking into consideration the LED and the pharmacokinetic characteristics of ABBV-951 (see Section 4.2). The investigator may adjust the prescribed infusion rate during visits to reach optimization of motor symptoms control. Subjects may choose their daily continuous infusion rate from 3 preprogrammed infusion rates. The investigator will determine and program the base daily infusion rate (F1) within the allowable range (0.17 to 1.04 mL/hr) and may program 2 additional infusion rates (F2 and F3) within a ± 20% limit from the prescribed base infusion rate. F2 should be an alternative higher continuous dose, and F3 should be an alternative lower continuous dose. F3 may be reduced beyond the 20% limit from the prescribed base infusion rate (F1) if medically necessary and only with approval from the AbbVie therapeutic area medical director (TA MD). If programmed, the alternative infusion rates (F2 and F3) must be within the allowable range (0.17 to 1.04 mL/hr). If the alternative infusion rates (F2 and F3) are not required, they must be programmed to "OFF." Subjects will receive a System User Manual that contains instructions for the daily management of their infusion.

Dermatologic Assessment

Subcutaneous delivery of study drug calls for attention during the procedures related to administration (general hygiene, skin disinfection, maintenance of a dirt-free environment while manipulating the system components, etc.), and subject training and adherence to proper techniques are critical. Manipulation at the level of the cannula pad due to disconnection and reconnection of the tubing might also lead to skin irritation, abrasion, and other lesions, which could evolve to infection and cellulitis because of bacterial contamination. Infusion site reactions including erythema, pain, or any other inflammation signs have been observed.[4] Most are mild or moderate in severity and resolve with treatment with antibiotics and interventions such as incision and drainage. Some cases might require further management and clinical correlation is recommended. Investigators should obtain dermatologic consult if needed.

Absorption of study drug by the subcutaneous tissue may vary depending on the volume of drug solution infused/day, skin characteristics, hydration, etc. Accumulation of study drug under the skin, manifesting as an elevated area of the skin, with or without induration and/or seepage of study drug from the infusion site after removal of the cannula or during infusion, might be a sign of reduced absorption, which could lead to irritation of the area and increased risk of bacterial contamination. In these cases, more frequent rotation of the infusion site (using a new cannula/infusion set) is recommended to minimize the risk of infection.

If any moderate to severe infusion site-related AE, such as cellulitis/abscess formation, ecchymoses, subcutaneous nodules, or scarring occurs, or if any infusion site-related reaction is assessed with an

irritation numeric grade equal to 7 on the Infusion Site Evaluation scale (see Section 3.6 of the Operations Manual [Appendix F]), the investigator or designee is instructed to do the following:

1. Photograph the skin reaction and follow the appropriate procedure for submission of photographs. In rare situations where an assessment or visit cannot be completed onsite due to an extenuating event (e.g., COVID-19-related conditions), the subject may be asked to obtain and submit a self-captured photograph of the skin reaction.
2. Refer the subject to a dermatologist for comprehensive evaluation (including skin biopsy if applicable), treatment, and follow-up per standard practice. The subject should be referred to a dermatologist within 2 business days after the photographs are taken. The dermatologic visit should be completed within 2 weeks from identification of the AE or skin reaction that meets the above criteria. While an in-person dermatology evaluation is preferred, this assessment may be performed as a telemedicine visit per the dermatologist's standard practice.

Post-Treatment Activities

Subjects who prematurely discontinue or are not enrolled in the extension study (M15-737) will receive a 30-day follow-up call after the end of infusion of study drug, if the subject is willing. See Section 5.7 for additional information.

4.2 Discussion of Study Design

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be used in this study. All efficacy measurements are qualified for assessing disease activity in subjects with PD.

Suitability of Subject Population

The subject population will consist of subjects with PD who report motor complications that are inadequately controlled by oral medications and who experience a minimum of 2.5 hours of "Off" time per day as assessed by PD diaries completed prior to enrollment/Day 1 (V3). Subjects must be on a stable oral PD medication regimen for at least 30 days prior to commencing ABBV-951.

Rationale for Selection of Therapeutic Dose Range

CD/LD remains the standard of care for PD. It is, however, recognized that the treatment of PD is highly individualized; both the treatments administered and their doses must be customized, based on the patients' signs and symptoms and their response to medication. In practice, this provides a wide distribution of patient doses, even within clinical trials.

In the LCIG double-blind, double dummy pivotal trial (Studies S187.3.001/S187.3.002), the median dose of levodopa was 1013 mg/day and the mean dose was 1117 mg/day for 16-hour daily infusion. These data represent a small subset of subjects where dosing was constrained to maintain the blinding of the study. Therefore, > 90% of subjects used less than 2000 mg over a 16-hour treatment period.

In the LCIG open-label safety study (Study S187.3.004), in which > 300 subjects were enrolled, the dosing was more reflective of clinical practice, where a significant proportion of subjects were able to simplify their therapy by discontinuing concomitant oral medications and maintaining only LCIG during the waking time. The LD doses from this study ranged from less than 500 mg/day to more than 3500 mg/day over a 16-hour treatment period (Table 1).

ABBV-951 is intended to be a 24-hour/day therapy (i.e., subjects will be exposed 8 more hours – or 50% longer – compared to LCIG exposure). The results of a pharmacokinetic study (Study M18-764) comparing LD plasma concentrations between LCIG plus LD/CD tablets and ABBV-951 in healthy volunteers demonstrated that LD from ABBV-951 is 8% more bioavailable than enterally-absorbed LD. Based on molecular weight (MW), 100 mg of LD are equivalent to 141 mg of levodopa phosphate (LDP).

Using these data, it is estimated that LD doses could range from less than 700 mg/day to about 4260 mg/day, over a 24-hour treatment period (approximately 1000-6000 mg LDP).

Table 1. LD Dose Distribution from LCIG Study S187.3.004

Distribution of LD Doses over 16 hours (mg)	Frequency		Cumulative Percent (%)	Estimated Doses over 24 hours	
	(N)	(%)		LD (mg)	LDP (mg)
< 500	1	0.3	0.3	695	1000
500 - 750	12	3.8	4.1		
750 - 1000	29	9.1	13.2		
1000 - 1250	48	15.1	28.4		
1250 - 1500	61	19.2	47.6		
1500 - 1750	53	16.7	64.4		
1750 - 2000	47	14.8	79.2		
2000 - 2250	22	6.9	86.1		
2250 - 2500	17	5.4	91.5		
2500 - 2750	13	4.1	95.6		
2750 - 3000	5	1.6	97.2		
3000 - 3250	4	1.3	98.4		
3250 - 3500	3	0.9	99.4		
> 3500	2	0.6	100.00	4260	6000
	Total: 317				

LCIG = levodopa-carbidopa intestinal gel; LD = levodopa; LDP = levodopa phosphate

4.3 Loading Dose, Continuous Infusion Rates, Titration, and Extra Doses

Oral Loading Dose

The purpose of the oral loading dose is to allow subjects to achieve symptom control quickly upon initiation of treatment. The loading dose for this study will be an oral dose of LD+DDCI corresponding as closely as possible to the subject's habitual first morning dose of LD+DDCI. Immediate-release formulations of LD+DDCI medications should be utilized for the oral loading doses.

Loading doses will be administered only once, at the initiation of ABBV-951 treatment, unless dosing is discontinued for ≥ 3 hours. Temporary disconnection (< 1 hour) for daily hygiene or to change empty syringes does not count as discontinuation and does not require a loading dose upon resuming the infusion (see Section 5.8).

Continuous Infusion Rate

Following the oral loading dose, ABBV-951 will be delivered continuously (24 hours daily) via an infusion set connected to a pump. Each subject's initial base continuous infusion rate (F1) will be calculated based on the subject's oral LD therapy over the 16-hour treatment period and an algorithm developed following a combination of pharmacokinetic and clinical considerations from ABBV-951 Phase 1 studies. A subject's baseline dose of immediate release (IR) LD+DDCI is the starting point for establishing the levodopa equivalent dose (LED) for dose selection (note: the levodopa contained in Stalevo® [CD/LD/entacapone] counts as IR). If a subject is not taking an IR formulation of LD+DDCI, the LED is calculated from the primary levodopa-containing medication. The conversion factors to use in calculating the total LED for dose selection are provided in Table 2 and are based on data from the literature.[2,3] The applicable calculation from Table 2 and a subject's baseline CD/LD IR dose should be added together to provide the total starting LED for ABBV-951 conversion.

Table 2. Levodopa Equivalent Dose Range

Medication	Conversion Factors to Calculate LED	
Controlled-release levodopa (e.g., Sinemet CR, Madopar CR)	For subjects taking controlled-release levodopa, **multiply** their daily dose of controlled-release levodopa **by 0.75** to obtain their LED.	
Extended-release levodopa (Rytary)	For subjects taking extended-release levodopa, **multiply** their total daily dose of Rytary by the appropriate conversion ratio in the following table to obtain their LED.	
	Rytary Dose Range (mg)	**Conversion Ratio (Rytary to LED)**
	0 – 855	**0.42**
	856 – 1755	**0.48**
	1756 – 2340	**0.56**
	2341 or above	**0.67**
Adjustment for subjects taking COMT inhibitors such as entacapone (e.g., Comtan or Stalevo) or tolcapone (e.g., Tasmar)	If subjects are taking tolcapone or entacapone, all LED calculated from the levodopa-containing products must be **multiplied by 1.33**. Note: The levodopa dose contained in Stalevo counts as IR.	

COMT = catechol-*O*-methyltransferase; CR = controlled release; IR = immediate release; LED = levodopa equivalent dose

Once a subject's daily LED has been determined, the starting infusion rate for ABBV-951 should be selected from Table 3. The continuous infusion rates below are estimated for the mid-point of the LED intervals provided and are designed to deliver therapeutic levodopa exposure. The ABBV-951 infusion will be delivered continuously via an infusion set connected to an ambulatory pump.

Table 3. Suggested ABBV-951 Starting Infusion Rate

LED From all Oral LD-Containing Medications Taken Over a Waking Time of 16 Hours (mg)[a]	Suggested ABBV-951 Starting Hourly Infusion Rate (mL/hr)[b]	Approximate Corresponding Hourly LD Amount (mg/hr)[c]
< 500	0.17	29
500 – 599	0.17 – 0.20	30 – 34
600 – 699	0.20 – 0.24	34 – 41
700 – 799	0.24 – 0.27	41 – 46
800 – 899	0.27 – 0.30	46 – 51
900 – 999	0.30 – 0.34	51 – 58
1000 – 1099	0.34 – 0.37	58 – 63
1100 – 1199	0.37 – 0.40	63 – 68
1200 – 1299	0.40 – 0.44	68 – 75
1300 – 1399	0.44 – 0.47	75 – 80
1400 – 1499	0.47 – 0.51	80 – 87
1500 – 1599	0-51 – 0.54	87 – 92
1600 – 1699	0.54 – 0.57	92 – 97
1700 – 1799	0.57 – 0.61	97 – 104
1800 – 1899	0.61 – 0.64	104 – 109
1900 – 1999	0.64 – 0.68	109 – 116
>2000	0.70	119

LD = levodopa; LED = levodopa equivalent dose; MW = molecular weight

a. Based on Table 2.

b. The suggested infusion rates are calculated for the mid-point of the interval to which they refer.

c. Based on the ABBV-951 concentration of LDP 240 mg/mL and MW conversion factor 100 mg LD = 141 mg LDP.

Titration

The ABBV-951 base infusion rate (F1) may be adjusted at the investigator's discretion at any time throughout the study to achieve and maintain an optimal therapeutic response for the individual subject, which means maximizing the functional "On" time during the day by minimizing the number and duration of "Off" episodes (bradykinesia) and minimizing "On" time with troublesome dyskinesia. Due to the capabilities of the infusion pump utilized in Study M15-741, the infusion rate must be increased or decreased by multiples of 0.01 mL/hr, corresponding to approximately 1.7 mg LD/hr, or approximately 40 mg LD over the 24-hour period. Therefore, an increase in the base infusion rate of 0.02 mL/hr will result in total increase of approximately 80 mg of LD over the 24-hour period. An increase of 0.04 mL/hr will result in a total increase of approximately 160 mg of LD over the 24-hour

period. A decrease of 0.06 mL/hr will result in a total decrease of approximately 240 mg of LD over the 24-hour period, etc.

Should the calculated daily LED from oral medications at Baseline (based on the 16-hour treatment period) for a subject be ≥ 2000 mg, the starting base infusion rate (F1) should be set at 0.70 mL/hr.

The investigator may decide to increase the infusion rate only after assessing the subject for clinical efficacy (achieving optimal therapeutic response, as defined above) and safety. The safety profile of ABBV-951 at doses higher than 200/4000 carbidopa phosphate/levodopa phosphate (CDP/LDP) resulting from infusion rates > 0.70 mL/hr will be assessed throughout the study via neurological examinations and physical assessment, as described in Appendix D. All AEs will be assessed, with particular attention to AESIs of polyneuropathy, weight loss, somnolence, and hallucinations/psychosis.

Alternative Continuous Infusion Rates (F2, F3)

Like other therapeutic approaches for PD, which require an individualized optimization, this study provides subjects the ability to select from alternative infusion rates within a specified range, if allowed by the investigator.

Two additional infusion rates (F2 and F3) may be preprogrammed into the pump by the investigator. F2 should be an alternative higher continuous dose, and F3 should be an alternative lower continuous dose. The additional infusion rates must be selected within a ± 20% limit from the prescribed base continuous infusion rate (F1). F3 may be reduced beyond the 20% limit from the prescribed base infusion rate (F1) if medically necessary and only with approval from the AbbVie TA MD.

Infusion rates lower than 0.17 mL/hr or higher than 1.04 mL/hr are not allowed.

If, during the study, the base daily infusion rate (F1) is programmed at 0.17 mL/hr, the alternative lower infusion rate (F3) must be disabled. If, at any point during the study the base daily infusion rate (F1) is programmed at 1.04 mL/hr, the alternative higher infusion rate (F2) and the extra dose option (see below) must be disabled.

The starting infusion rate must not be higher than 0.70 mL/hr; adjustments may be done only after clinical assessment (neurological and physical examination).

If the alternative infusion rates (F2 and F3) are not required, the investigator or his/her designee must disable them by programming them to "OFF" and the subject will not be able to choose alternative infusion rates. If the investigator enables these options, the subject may select the infusion rate from these 3 preprogrammed choices (F1, F2, or F3) and will be required to record on the dosing diary the time of the day when they change the infusion rate. The numerical values of the infusion rates cannot be modified by the subjects.

Extra Doses

If the investigator allows it, subjects may self-administer extra doses of ABBV-951 during the course of the 24 hours to address immediate medical needs, such as the rapid deterioration of motor function. The ability to self-administer extra doses, the extra dose volume and lockout time (the interval between extra doses) are determined and programmed by the investigator or his/her designee and cannot be modified by the subjects. The investigator can choose the volume of the extra doses from the following

options: 0.11, 0.15, 0.19, 0.24, or 0.3 mL (which are equivalent to ~20, ~25, ~33, ~40, and ~50 mg of levodopa, respectively). The lockout time is programmable from 1 hour to 24 hours in 15-minute increments; the minimum lockout duration is 60 minutes. If the investigator elects not to allow the use of extra doses, this function can be disabled by setting the volume to "0.00."

If the extra dose function is enabled, subjects are required to record on the dosing diary the time of the day when they self-administered an extra dose. Dosing diaries will be reviewed by the study personnel at every study visit.

If the need for extra doses is greater than 5 times per day, the investigator should consider increasing the base infusion rate and increasing the lockout time to limit the number of extra doses per day. If at any time in the study F1 or F2 are set at 1.04 mL/hr, the extra dose option should be disabled. Doses of LDP higher than 6000 mg/24 hr (equivalent to 4260 mg LD/24 hr) are not allowed under any circumstances during the study.

The investigator should consider this upper limit when programming alternative infusion rates and/or volumes and lockout time of extra doses. Guidance is provided in Table 4.

Table 4. Guidance for Alternative Infusion Rate Limits and Number of Extra Doses Based on Base Continuous Infusion Rate

F1 Base Infusion Rate (mL/hr)	F2 Upper Limit (mL/hr)	F3 Lower Limit (mL/hr)	Maximum Number of Extra Doses Allowed[a]
0.17	≤ 0.20	OFF	23
0.2	≤ 0.24	≥ 0.17	23
0.23	≤ 0.28	≥ 0.18	23
0.27	≤ 0.32	≥ 0.22	23
0.3	≤ 0.36	≥ 0.24	23
0.33	≤ 0.40	≥ 0.26	23
0.37	≤ 0.44	≥ 0.30	23
0.4	≤ 0.48	≥ 0.32	23
0.43	≤ 0.52	≥ 0.34	23
0.47	≤ 0.56	≥ 0.38	23
0.5	≤ 0.60	≥ 0.40	23
0.53	≤ 0.64	≥ 0.42	23
0.57	≤ 0.68	≥ 0.46	23
0.6	≤ 0.72	≥ 0.48	23
0.63	≤ 0.76	≥ 0.50	23
0.67	≤ 0.80	≥ 0.54	19
0.7	≤ 0.84	≥ 0.56	16
0.73	≤ 0.88	≥ 0.58	13
0.77	≤ 0.92	≥ 0.62	9
0.8	≤ 0.96	≥ 0.64	7
0.83	≤ 1.00	≥ 0.66	4
0.86	≤ 1.02	≥ 0.69	1
0.89	≤ 1.04	≥ 0.71	0

F1 Base Infusion Rate (mL/hr)	F2 Upper Limit (mL/hr)	F3 Lower Limit (mL/hr)	Maximum Number of Extra Doses Allowed[a]
0.92	≤ 1.04	≥ 0.74	0
0.95	≤ 1.04	≥ 0.76	0
0.98	≤ 1.04	≥ 0.78	0
1	≤ 1.04	≥ 0.80	0
1.04	OFF	≥ 0.83	0

a. Values provided for the highest possible extra dose volume (0.3 mL), assuming the higher alternative infusion rate (F2) option is enabled and set at its upper limit, and assuming lock-out time set at its minimum value of 60 minutes (hence allowing 23 extra doses/day).

Conversion Algorithm

The conversion algorithm was created taking into consideration the MW of LDP, drug product concentration, daily 24-hour exposure time, and pharmacokinetic data from ABBV-951 Phase 1 studies.

In a 4-week clinical study in aPD patients (Study M15-739), an algorithm to convert oral LD to ABBV-951 was created, based on a combination of pharmacokinetic and clinical considerations. The results of Study M18-764, together with the evaluation of the pattern of dose adjustments from Study M15-739, confirmed the appropriateness of this algorithm to achieve adequate control of motor symptoms in PD patients. Therefore, the current study will utilize a similar approach to convert oral LD to ABBV-951 as in the 4-week study (Study M15-739).

Assumptions Used to Generate the Algorithm

Most PD patients are treated with oral PD medications during their waking time; therefore, the calculated LED reflects the dopaminergic need during the average 16-hour treatment period. ABBV-951 is administered over 24 hours, so 50% more drug is added to account for the additional 8 hours of treatment. Additionally, from pharmacokinetic studies comparing LD plasma concentrations between LCIG and ABBV-951, it appears that ABBV-951 is more bioavailable than enterally-absorbed levodopa. Finally, a conversion factor of oral levodopa to LDP was determined to be 1.41 based on differences in MW.

One mL of the ABBV-951 drug product used in this study contains 240 mg of LDP and 12 mg of carbidopa phosphate (CDP). Once the total need of LDP per day has been calculated, it is divided by 240 mg to determine the number of milliliters needed per day, and then divided over 24 hours to establish an infusion rate. Each suggested infusion rate is calculated for the midpoint of the LED range represented in Table 3.

Guidance for Enabling Alternative Infusion Rate and Extra Dose Options

Like other individualized treatments, considering the extensive knowledge that aPD patients have about recognizing whether PD symptoms are sufficiently controlled by their therapy, this study provides subjects the ability to select from alternative infusion rates within a specified range, if allowed by the investigator.

The investigator should consider whether to enable alternative infusion rates and extra doses and provide those options to subjects, based on his/her clinical judgment of the subject's cognitive performance, compliance, and personality traits.

Allowing an alternative higher infusion rate (F2) could facilitate refining the base continuous infusion rate during the optimization period. Subjects who report troublesome dyskinesia, freezing of gate, or nocturnal akinesia at baseline are often treated with sub-optimal oral daily doses of LD.[5,6] In these cases, programming F1 as suggested in Table 3 could result in a sub-optimal dose of ABBV-951. The investigator may program F2, starting with small increments (e.g., 5% – 10%), and enable subjects who feel underdosed to switch to the alternative higher infusion rate. Similarly, if subjects are expected to sustain extended physical activity (e.g., sport) or require higher doses of levodopa at a specific time of day, F2 could be temporarily selected to account for the higher dopaminergic demand. Also, if subjects require more than 5 extra doses during the day, they may be instructed to switch to F2 and reduce the use of extra doses, while waiting for of the investigator to adjust the base infusion rate at the next study visit after reviewing the dosing diary. It is important that subjects be reminded to log on the dosing diary any time they self-administer an extra dose or switch the infusion rate to one of the enabled options.

If the investigator prefers not to provide this option or considers the subject not suitable to choose among the provided options, he/she should disable the alternative higher infusion rate by programming it to "OFF."

Investigators may consider whether to allow subjects to switch to an alternative lower infusion rate (F3) before going to bed, if subjects report no complaints of nocturnal akinesia or nighttime symptoms at baseline or if subjects have known history of impulse control disorders or nocturnal hallucinations.[6-8] Additionally, data suggest that the low variability and fluctuations in plasma LD exposure from continuous delivery may translate in an average reduction of efficacious daily levodopa doses;[9] hence, if between visits during the optimization period, subjects experience sustained dyskinesia, they may be instructed to select the alternative lower infusion rate and record it in their dosing diary, until the investigator adjusts the base parameters at the following study visit. The alternative lower infusion rate, F3, may be programmed to be up to 20% lower than F1. F3 may be reduced beyond the 20% limit from the prescribed base infusion rate (F1) if medically necessary and only with approval from the AbbVie TA MD.

If nocturnal akinesia is present or if bothersome nighttime symptoms exist, investigators should consider maintaining the base infusion rate (F1) consistent for the 24 hours and disable the option for the alternative lower infusion rate (programming it to "OFF"). Similarly, if the investigator prefers not to provide this option or considers the subject not suitable to choose among the provided options, he/she should disable the alternative lower infusion rate by programming it to "OFF."

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

All subjects will be evaluated to ensure that they meet the eligibility criteria at Screening Visits 1 and 2 (V1 and V2) and prior to enrollment on Day 1 (V3).

Consent

1. Subject must be able to understand the nature of the study and have had the opportunity to have any questions answered by the investigator.
2. Subject, if judged by the investigator to have decision making capacity, must voluntarily sign and date an informed consent form approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to initiation of any study-specific procedures.

Demographic and Laboratory Assessments

3. Subject must be an adult male or female, 30 years of age, or older.
4. Subject is willing and able to comply with procedures required in this protocol.
5. Subject does not have a low vitamin B_{12} level (< 200 pg/mL); or does not have low-normal vitamin B_{12} level (< 300 pg/mL) with elevated methylmalonic acid (MMA > 0.41 µmol/L) at Screening Visit 1 (V1).[a]
6. Subject has normal cognitive function (Mini-Mental State Examination [MMSE] score of 24 or greater). Subjects with mild cognitive impairment (MMSE score of 19 – 23 inclusive) may be enrolled if in the investigator's opinion, are able to adhere to all study requirements. Subjects with moderate or severe impairment (MMSE scores of 18 or below) may not be enrolled.
7. Subject is not considered by the investigator to be an unsuitable candidate to receive ABBV-951 for any reason.

Disease Activity

8. Subject must have a diagnosis of levodopa-responsive idiopathic PD.
9. Subject must meet the following disease activity criteria:
    - Must be taking a regimen of oral medications for PD that has remained unchanged for at least 30 days before commencing ABBV-951 (rescue medications taken "as needed" may be disregarded when assessing whether the regimen of oral medications has remained unchanged); this regimen must include levodopa-containing formulations such as CD/LD IR (e.g., Sinemet, Madopar), CD/LD-CR (e.g., Sinemet controlled release [CR]), CD/LD extended release (e.g., Rytary), CD/LD/entacapone (e.g., Stalevo).
    - Must have a recognizable/identifiable "Off" and "On" state (motor fluctuations) as established through investigator observation and confirmed by PD diary entries recorded during the concordance test performed during the Screening Period.[b]
10. Must be judged to be inadequately controlled by current therapy in the opinion of the investigator and experience a minimum of 2.5 hours of "Off" time per day as assessed by PD Diary prior to Day 1 (V3). Subjects who have received DBS therapy are eligible for the study, provided they are considered stable, are still levodopa responsive, and meet all other eligibility criteria.

Subject History

11. Subject does not have a history of significant skin conditions or disorders (e.g., psoriasis, atopic dermatitis) or evidence of recent sunburn, acne, scar tissue, tattoo, open wound, branding, or colorations that in the investigator's opinion would interfere with the infusion of study drug or could interfere with study assessments.[c]
12. Subject does not have a recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.
13. Subject does not have significant current suicidal ideation within 1 year prior to study drug administration as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at either screening visit, or any history of suicide attempts within the last 2 years.
14. Subject does not have a history or presence of psychotic episodes that in the investigator's judgment are not adequately controlled by second generation (atypical) antipsychotics and that could preclude adherence to the protocol.
15. Subject does not have other clinically significant unstable medical conditions or any other reason that the investigator determines would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
16. Subject does not have a history of allergic reaction or significant sensitivity to levodopa or constituents of the study drug (and its excipients) and/or other products in the same class.
17. Subject does not have any known medical condition for which levodopa is contraindicated (e.g., suspicious undiagnosed melanoma, narrow-angle glaucoma, severe heart failure, severe cardiac arrhythmia, pheochromocytoma, untreated hyperthyroidism, or Cushing's syndrome and other circumstances where adrenergics are contraindicated).
18. Subject has not donated or lost 550 mL or more blood volume (including plasmapheresis) or received a transfusion of any blood product within 8 weeks prior to initial study drug administration.
19. Subject has no known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection or known exposure to a confirmed case of COVID-19 infection during 14 days prior to Screening.
    - Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 viral clearance criteria:
        - Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
        - Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects).

- Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Contraception

20. If female of childbearing potential, subject must have a negative serum pregnancy test at Screening Visit 1 (V1) and a negative urine pregnancy test on Day 1 (V3) prior to the start of the infusion of study drug. Female subjects of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2) at Screening Visit 1 (V1) do not require pregnancy testing.
21. If female, subject must be either **postmenopausal**, OR permanently **surgically sterile** OR for women of childbearing potential (WOCBP) practicing at least 1 protocol-specified **method of birth control**, that is effective from Day 1 (V3) through at least 30 days after the end of the infusion (end of Treatment Period).
22. If male and **sexually active with female partner(s) of childbearing potential**, subject must agree, from Day 1 (V3) through 30 days after the end of the infusion of study drug, to practice protocol-specified contraception.
23. If female, subject is not pregnant, breastfeeding, or considering becoming pregnant or donating eggs during the study or within 30 days after the end of the infusion of study drug.
24. If male, subject is not considering fathering a child or donating sperm during the study or within 30 days after the end of the infusion of study drug (end of Treatment Period).

Concomitant Medications

25. Subject has not received an investigational product other than ABBV-951 within a time period equal to 5 half-lives, if known, or within 6 weeks, whichever is longer, prior to study drug administration.

a. *Subjects with a low vitamin B_{12} or low-normal vitamin B_{12} and high MMA plasma level may undergo supplemental vitamin therapy. A re-test for vitamin B_{12} is allowed within the Screening Period without repeating other screening procedures. Subjects with normal vitamin B_{12} or low-normal vitamin B_{12} without elevated MMA plasma level at re-test are eligible for enrollment. If a subject is rescreened due to vitamin B_{12} deficiency, all screening procedures, with the exception of the PD diary concordance test, will need to be repeated to be eligible for enrollment.*

b. *The PD diary concordance test may be omitted for subjects previously enrolled in Study M15-739, for whom recognizable/identifiable "Off" and "On" state (motor fluctuations) have been already established and confirmed. The PD diary concordance test may also be omitted for subjects for whom recognizable/identifiable "Off" and "On" state (motor fluctuations) have been already established and confirmed, and for unforeseen circumstances, require rescreening.*

c. *Subjects with evidence of transient skin conditions such as recent sunburn or open wound that resolved within the Screening Period are eligible for enrollment.*

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-childbearing Potential

  Females of non-childbearing potential do not need to use birth control during or following study drug treatment if considered to be of non-childbearing potential due to any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy during study drug infusion and for at least 30 days after the end of the infusion. Females of childbearing potential must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal*, transdermal*, injectable*) associated with the inhibition of ovulation, initiated at least 1 month prior to Day 1.
    - Progestogen-only hormonal contraception (oral, injectable*, implantable*) associated with inhibition of ovulation, initiated at least 1 month prior to Day 1.
    - Bilateral tubal occlusion/ligation (can be hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized sexual partner(s): The vasectomized partner(s) has received medical assessment of the surgical success and is the sole sexual partner of the study subject.
    - True abstinence, defined as refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

* *Not approved in Japan.*

Contraception Requirements for Males

Male subjects who are sexually active with a woman of childbearing potential, even if the male subject has undergone a successful vasectomy, must agree from Day 1 (V3) through at least 30 days after the end of the infusion to:

- Use condoms

  AND

- His female partner(s) must use at least one of the following methods of birth control:
  1. Combined (estrogen and progestogen-containing) hormonal birth control (oral, intravaginal*, transdermal*, injectable*) associated with inhibition of ovulation initiated at least 1 month prior to Day 1
  2. Progestogen-only hormonal birth control (oral, injectable*, implantable*) associated with inhibition of ovulation initiated at least 1 month prior to Day 1
  3. Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
  4. IUD
  5. IUS

* *Not approved in Japan.*

5.3 Prohibited Medications and Therapy

The medications listed in Table 5 are prohibited during the Treatment Period.

Table 5. Prohibited Medications

Apomorphine[a,b]
Dopamine-depleting agents (such as, but not limited to, reserpine, tetrabenazine, amphetamines)
MAO-A inhibitors and other non-selective MAO inhibitors[c]
Ergot dopamine agonists (lisuride, bromocriptine, cabergoline, etc.)
Dopamine antagonist or partial agonist, first generation antipsychotics, antiemetic medications, and second-generation antipsychotic with higher dopamine receptors interaction (such as, but not limited to, fluphenazine, loxapine, perphenazine, thiothixene, haloperidol, metoclopramide, aripiprazole, asenapine, risperidone, paliperidone, perospiron)
Oral and/or inhaled medications containing levodopa[a,d]
COMT inhibitors (such as entacapone, tolcapone, opicapone)[a]

COMT = catechol-*O*-methyltransferase; DDCI = DOPA decarboxylase inhibitor; IR = immediate release; LD = levodopa; MAO = monoamine oxidase

a. Allowed during the Screening Period; must be discontinued for at least 12 hours before commencing ABBV-951 and is prohibited for the duration of the Treatment Period.

b. Apomorphine for continuous subcutaneous delivery (approved in Europe) must be discontinued 30 days before commencing ABBV-951.

c. Non-selective MAO inhibitors are contraindicated for use with levodopa and should not be taken by study subjects. MAO inhibitors with selectivity for MAO type B (e.g., rasagiline, selegiline, safinamide) are allowed.

d. LD+DDCI IR or levodopa inhalation powder is allowed in case of serious medical need such as in the case of pump malfunction.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccine, over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from 30 days prior to the time of screening (V1) or receives during the study must be recorded through the end of the study.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with ABBV-951 is located in the ABBV-951 Investigator's Brochure.[1]

With the exception of the Optimization Period, subjects should remain on stable anti-PD medication for the duration of the study, unless medically needed.

All subjects should fill a prescription provided by the investigator or their general practitioner for oral LD+DDCI IR tablets or levodopa inhalation powder in case rescue therapy is needed. Once ABBV-951 treatment has been initiated, rescue tablets or the inhalation powder capsules should only be used in the case of a serious medical need, such as rapid deterioration of motor symptoms that do not respond to an extra dose of ABBV-951 or to an increase in the preset infusion rate. The subject should be instructed to record all oral levodopa tablets or inhalations on the Subject Dosing Diary on the assigned days.

The following concomitant (Table 6) and rescue (Table 7) medications are allowed:

Table 6. Allowed Concomitant Medications/Therapy

Non-ergolinic dopamine agonists[a] (pramipexole, ropinirole, rotigotine)
Selective MAO-B inhibitors (e.g., rasagiline, selegiline)
Amantadine (IR and ER formulations)
Safinamide
Zonisamide[b]
Istradefylline[b,c]

ER = extended release; IR = immediate release: MAO = monoamine oxidase

a. Apomorphine and ergot dopamine agonists (lisuride, bromocriptine, cabergoline, etc.) are NOT allowed.

b. Approved in Japan.

c. Approved in the United States.

Table 7. Allowed Rescue Medications/Therapy

100 mg of oral LD+DDCI (e.g., Sinemet 25/100). The DDCI may vary, based on the country of interest (e.g., benserazide vs. carbidopa; 10 mg vs. 25 mg, etc.) **84 mg of levodopa inhalation powder (e.g., 2 capsules of Inbrija)**[a]	• Allowed as rescue therapy (e.g., in the case of pump malfunction)

DDCI = DOPA decarboxylase inhibitor; LD = levodopa

a. Approved in the United States.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Subject answers "yes" to question 4 and/or question 5 on the suicidal ideation portion of the C-SSRS and/or positive responses to any category of the suicidal behavior portion of the C-SSR; these subjects should be referred for appropriate follow-up care and the AbbVie TA MD should be notified.

For subjects considered to be lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

Refer to the Operations Manual in Appendix F for details on how to handle study activities/procedures.

5.6 Temporary Suspension of Study Drug Treatment

A subject's study drug treatment may need to be temporarily suspended for medical reasons (i.e., illness, hospitalization). If such a situation occurs, subjects who experience a suspension up or equal to 30 days in duration may be reinitiated on study drug at the discretion of the investigator. A suspension of study drug, greater than 30 days in duration, will require approval from the AbbVie TA MD prior to drug being restarted.

5.7 Follow-Up After Subject Discontinuation of Study Drug or From Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they prematurely discontinue treatment with study drug.

If a subject prematurely discontinues study participation and is willing, the procedures outlined for the Premature Discontinuation Visit (Appendix D) should be completed as soon as possible, preferably within 2 weeks. In addition, if a subject discontinues study participation or completes the study but will not participate in the extension study and is willing, a 30-day follow-up phone call after the end of the infusion of study drug will be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

5.8 Study Drug and Study Devices

The investigational product consists of study drug (solution for infusion) and study devices. Some of the devices specified below are approved in some countries in which this study will be conducted; however, will be labeled for investigational use. Information about the ABBV-951 formulation and devices to be used in this study are presented in Table 8 and Table 9, respectively.

Table 8. Identity of Study Drug

Study Drug	Dosage Form	Deliverable Content per Vial	Manufacturer
ABBV-951 12/240 mg/mL (CDP4´/LDP4´) S.INF. 15 mL	Solution for infusion	180 mg/3600 mg (CDP4´/LDP4´)	AbbVie

CDP4 = carbidopa phosphate 4; LDP4 = levodopa phosphate 4; S.INF = solution for infusion

Table 9. Identity of Study Devices

Description	Usage	Manufacturer	Model Number
Crono PAR Series 3 Pump[a]	Delivery of ABBV-951	Canè S.p.A. Medical Technology	CRONO PAR V3
20 mL syringe without needle	Delivery of ABBV-951	Canè S.p.A. Medical Technology	CRN/20/WN
Neria Guard infusion set, 6 mm cannula, 60 cm tubing[b]	Delivery of ABBV-951	Unomedical A ConvaTec Company	Unomedical reference #: 704060-5226 USA (US) 704060-5226 (OUS)
Neria Guard infusion set, 9 mm cannula, 60 cm tubing[b]	Delivery of ABBV-951	Unomedical A ConvaTec Company	Unomedical reference#: 704060-5229 USA (US) 704060-5229 (OUS)
Cleo 90 infusion set, 6-mm cannula with inserter, 24-inch tubing with buckle	Delivery of ABBV-951	Smiths Medical	21-7220-24
Cleo 90 infusion set, 9-mm cannula with inserter, 24-inch tubing with buckle	Delivery of ABBV-951	Smiths Medical	21-7230-24
Vial adapter	Facilitates transfer of ABBV-951 to syringe/reservoir	West Pharmaceutical Services	West Item ID: 36098056 Medimop Cat #: 8073005

OUS = Outside United States; US = United States; V = Visit

a. Software version "DL.v01.05" is installed on the pumps.

b. Subjects enrolled under protocol v6.0 (or after) will use the Neria Guard infusion set at the start of enrollment (Day1/V3). Subjects may transition between Neria Guard and Cleo 90 if the investigator determines this to be clinically necessary. Subjects enrolled prior to protocol v6.0 may continue to use the Cleo 90 infusion set or transition to Neria Guard at the investigator's discretion.

The pump comes in a kit form that includes Canè mini suitcase, Canè elastic belt, Canè collar strap, Canè fabric case, Canè Battery Compartment opener tool.

Clinical study personnel will receive the System User Manual and System Programming Guide. Subjects will receive the ABBV-951 System User Manual and Placemat guide for daily use.

Subject dosing will be recorded in a subject dosing diary for 2 consecutive days prior to any study visits as specified in the study activity schedule in Appendix D. The subject will be instructed on how to return all drug containers (even if empty), devices and ancillaries. Clinical study personnel will document compliance.

Treatments Administered

Subjects will receive an oral loading dose of CD/LD on Day 1 (V3), followed by a 24-hour daily CSCI of ABBV-951.

The oral loading dose will be determined by the investigator per therapeutic management prior to infusion. The infusion rate of ABBV-951 (and therefore the total amount of ABBV-951 administered) will be calculated based on the subject's levodopa equivalent dose (LED) and an ABBV-951 conversion algorithm. The initial dose of study drug and corresponding infusion rate can be adjusted during the Optimization Period to reach the individualized therapeutic dose that most adequately controls the subject's motor symptoms as assessed by the investigator through subject interviews and/or other evaluations of symptom severity. The ABBV-951 basal infusion rate can also be adjusted throughout the study at the discretion of the investigator. The investigator may preprogram 3 infusion rates into the pump, 1 that corresponds to the base prescribed daily infusion rate (F1) and 2 additional infusion rates (F2 and F3) that are programmable within a ± 20% limit from the prescribed base infusion rate and always within the allowable range (0.17 to 1.04 mL/hr); F2 should be an alternative higher continuous dose and F3 should be an alternative lower continuous dose. F3 may be reduced beyond the 20% limit from the prescribed base infusion rate (F1) if medically necessary and only with approval from the AbbVie TA MD. If the alternative infusion rates (F2 and F3) are not required, the investigator or his/her designee must program them to "OFF." Thus, subjects might have the freedom to choose among the preprogrammed infusion rates or to self-administer extra doses of ABBV-951 during the day, per the investigator's judgment. The pump will be programmed by the site per instructions in the System Programming Guide.

During the Treatment Period, the ABBV-951 infusion will be self-administered by the subject using study devices (i.e., infusion set connected to an infusion pump) indicated for subcutaneous delivery. The drug delivery system will need to be loaded with the investigational drug at the same time every day for subjects who require 1 vial per day (every 24 hours), or at the same times of the day (every 12 hours) for subjects who require 2 vials per day. To prepare the drug delivery system, reference the System User Manual instructions: study drug will be loaded into a syringe that will then be connected to the pump. The infusion site will be prepared. The insertion device will be used to insert the cannula and apply the cannula pad to the skin. The infusion set tubing will be attached to the syringe, primed, and then attached to the cannula pad on the subject. The daily dose will be initiated by starting the pre-programmed pump. When vial changes are performed, depending on how long the infusion set has already been in use, subjects may need to either: a) obtain all new components or b) obtain all new components except for a new infusion set (i.e., infusion set tubing and insertion device/cannula pad, which can be used up for 3 consecutive days). For the latter situation, the subject will use a new syringe and a new vial adapter to draw their therapy from a new vial, connect the new syringe to the pump, connect their existing infusion set to the syringe, and start their therapy.

The infusion set and the infusion site (area of the skin where the subcutaneous cannula is inserted) can be left unchanged for up to 3 days when the drug is infused continuously. This includes maintaining the same infusion set when changing empty syringes or using a new vial (for those who require two vials per day). However, a new vial adapter and a new syringe are required any time a new vial is used. The infusion set should be changed, and the infusion site rotated every 3 days unless a more frequent rotation schedule is medically indicated (investigators should consider instructing the subject to rotate the infusion site more frequently than every 3 days (e.g., every 2 days or every day) if skin irritation and/or drug pooling is observed). Temporary interruptions of study drug are allowed (e.g., for hygiene, or changing empty syringes). A change in vial, vial adapter, syringe and infusion set, and rotation of the infusion site are required before resuming infusion for interruptions longer than approximately 1 hour. If study drug is interrupted for approximately 3 hours or more, a loading dose is recommended to quickly achieve symptomatic control (see table below):

Duration of drug suspension	Use new entire infusion set	Use new vial/new vial adapter/new syringe	Rotate infusion site	Self-administer oral dose
1 to < 3 hours	✓	✓	✓	None
≥ 3 hours	✓	✓	✓	Loading dose[a]

a. An oral dose of immediate-release formulations LD+DDCI corresponding as closely as possible to the subject's habitual first morning dose taken prior to commencing ABBV-951.

The investigator will select the length of the infusion set cannula among those provided, considering individual subject characteristics such as thickness of the abdominal subcutaneous fat tissue. The appropriate cannula will be long enough to deliver study drug solution to the subcutaneous tissue without infiltrating the muscle wall, which can cause pain and/or occlusion of the cannula.

The infusion should be administered to a site with ample subcutaneous tissue and at least 5 centimeters (or 2 inches) away from the site of application of ECG electrodes, and at least 5 centimeters (or 2 inches) away from the umbilicus (if the selected area for infusion is the abdomen). Infusions should not be administered to areas of scarred or hardened tissue or stretch marks, to skin folds or creases where the body naturally bends a great deal, or to areas where clothing might cause irritation (e.g., near the beltline).

In the event of an infusion pump malfunction or other event that temporarily prevents delivery of study drug, the time period during which study drug was not delivered will be recorded by the site, in the electronic data capture system. The subject should call the clinical study personnel, so that they may attempt to resume the study drug infusion. The time that the infusion stopped and/or malfunction will be recorded to the minute if known (otherwise, an estimated time will be recorded). If the infusion is resumed, the restart time will be recorded to the minute. If the study drug infusion is not able to be resumed or if the investigator is concerned that the subject may not be able to successfully complete the study drug infusion requirements, the subject may be discontinued from the study.

Alternative Infusion Site Locations

Although the abdomen is the preferred infusion site location, situations may occur where an alternative infusion site may need to be considered for a subject. If the investigator believes that an alternative infusion site is needed for a particular subject, for example, due to abdominal skin reactions that do not heal fast enough to allow for rotation, surgical interventions, scar tissue, or anatomical restrictions, the following alternative sites may be considered after obtaining approval from AbbVie TA MD:

- Thighs: anterior (both lateral and medial)
- Arms: posterior (both lateral and medial)
- Flanks

Investigators should factor in the following when considering one of these sites:

- Body composition and distribution of subcutaneous tissue: look for places on the skin where you can "pinch an inch" to ensure there is adequate subcutaneous tissue (e.g., for males, more around the abdomen; for females, more around hips and upper thighs).

- Ability to use alternative infusion site. It might be difficult for subjects to apply the cannula to the flank or to the dominant arm by themselves.
- Hirsutism: to minimize issues with adhesiveness of cannula pad, avoid areas with excess hair or consider removing hair without causing blade-related skin trauma. If shaving with razor, consider doing 1 day or 2 days prior to cannula insertion. Alternatives to razor shaving are trimming or use of hair removal creams.
- Sweating: to minimize issues with adhesiveness of cannula pad and risk of folliculitis (especially if blade-shaven), avoid areas where the subject sweats significantly and avoid tight-fitting clothes on the chosen area. Also consider using commercially available ancillary adhesive materials.
- Sleep position: discuss expectation with subject to either adjust sleeping position or consider an alternative location that does not impact sleep habits.
- Physical activity and exercise: consider choosing sites with the least risk of being impacted by the physical activity and consider using ancillary adhesive materials to prevent activity-related dislodgement of the cannula and subsequent inadequate infusion delivery (intradermal rather than subcutaneous). Avoid sunscreen or lotion on the area and if used, ensure the area is cleaned with alcohol pad/wipes and allowed to dry completely before inserting the cannula.
- Subject preference: subject's desire for cannula concealment (thigh and flank) versus no concealment (arm).

The alternative infusion site(s) may be used sporadically or integrated into the routine with the abdomen rotation at the investigator's discretion. If an alternative site is used exclusively long term, it is preferable to alternate (right/left) and maintain the 2.5-cm (1-inch) distance from the previous infusion site when returning to the same side. Sites will record information in subject's source documentation on the alternative infusion site(s) used.

Packaging and Labeling

ABBV-951 will be supplied as solution for infusion in vials in an open-labeled fashion and packaged in a carton containing 6 vials per carton. ABBV-951 will be labeled as ABBV-951 12/240 mg/mL (CDP4´/LDP4´) S. INF. 15 mL Vial. Each vial and carton will be labeled as required per country requirements. Each label must remain affixed to the vial and carton.

AbbVie will supply ABBV-951 and the study pump, its accessories, syringe/drug reservoir, infusion sets, and vial adapters. Non-investigational medicinal products (e.g., rescue therapy with LD+DDCI IR tablets or levodopa inhalation powder) must be obtained commercially, unless local regulations require the sponsor to provide them.

Storage and Disposition of Study Drug

ABBV-951 must be stored under refrigeration between 2°C to 8°C (36°F to 46°F) and must be protected from light. ABBV-951 must be allowed to warm in the sealed vial to room temperature for 30 minutes prior to transfer to the drug reservoir/syringe. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label (refrigerated) until the time of use or until returned to AbbVie.

Tote bags, cold packs, cooler bags, disposal containers, and alcohol swabs, may be provided to study subjects. Batteries might be provided by AbbVie, based on country-specific regulations and will be locally sourced.

The drug delivery system, including the infusion pump, infusion set, and syringes, must be used as indicated and training will be provided to the clinical study personnel and/or a home care nurse provided by the sponsor. Detailed instructions for the use of the drug delivery system pump are listed in the pump ABBV-951 System User Manual and the ABBV-951 System Programming Guide.

Subject Identifier Assignment

An interactive response technology (IRT) system will assign a unique identification number to each subject at Screening Visit 1 (V1). For subjects who do not meet the study selection criteria, clinical study personnel must register the subject as a screen failure in the IRT system.

For subjects who rescreen (e.g., due to Vitamin B_{12} deficiency), the screening number assigned by the IRT at the initial screening visit should be used. Treatment will be administered in an open-label manner.

Subjects who are enrolled will retain the subject number assigned to them at Screening Visit 1 (V1) throughout the study.

Contact information and user guidelines for the IRT use will be provided to each site.

Selection and Timing of Dose for Each Subject

A CSCI of study drug will be delivered over 24 hours daily for up to 52 weeks via an infusion set connected to a pump. Each subject's base continuous infusion rate (F1) will be initially calculated based on the subject's daily LED and an algorithm developed following the analysis of pharmacokinetic data from Phase 1 studies. The dose should be adjusted based on the clinical response for the individual subject, which means maximizing the functional "On" time during the day by minimizing the number and duration of "Off" episodes (bradykinesia) and minimizing "On" time with disabling dyskinesia.

Study Drug/Study Devices Accountability

The investigator or his representative will verify that study drug and study devices are received intact and in the correct amounts. This will be documented by signing and dating a proof of receipt or similar document. A current (running) and accurate inventory of study drug and study devices will be maintained in the IRT system. For those subjects who are allowed to benefit from a direct to patient shipment of the study drug and study devices, the third-party vendor contracted by the sponsor may be responsible of those steps described above.

Subjects will be instructed to return used drug vials with vial adapters attached within the original vial carton; subjects will also be instructed to return unused vials in the original vial carton. Used syringes, infusion sets (inserter and infusion set tubing) will be collected into a disposal container and returned to the study site for proper disposal or an alternative sponsor-approved method of disposal shall be used. Unused syringes, infusion sets (inserter and infusion set tubing) and vial adapters will be returned by the subject to the site at the end of the study. At the end of the study, subjects will be instructed to return the pumps, and the sites would reconcile the pump in the IRT system.

Site personnel will review returned study drug kits, empty study drug packaging, devices, and ancillaries to verify compliance at each visit. Returned study drug kits will be reconciled in IRT at each visit. Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and lot numbers for all non-investigational products (e.g., rescue therapy with LD+DDCI IR tablets or levodopa inhalation powder) dispensed by the site. Returned study drug should not be re-dispensed to the subject.

Upon completion or termination of the study, all original containers (containing unused investigational product) will be returned to AbbVie or destroyed on site, according to instructions from AbbVie and according to local regulations.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying the IEC/IRB, regulatory authorities (as applicable) and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the drug component of the product or to the medical device components.

This may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

For medical devices, a product complaint also includes:

- All deaths of a subject using the device
- Any illness, injury, or AE in the proximity of the device
- An AE that could be a result of using the device
- Any event needing medical or surgical intervention including hospitalization while using the device
- Malfunctions, use errors, or inadequacy in the information supplied by the manufacturer

Medical Complaints/Adverse Events and Serious Adverse Events: Study Drug

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

Investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was planned prior to study entry; however, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not

Disability/Incapacity	intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the start of study drug infusion until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Reactions and Serious Adverse Reactions

An adverse reaction (AR) implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An AR, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Serious adverse reactions (SARs) are defined as all noxious and unintended responses to an investigational medicinal product (IMP) related to any dose administered that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.

A suspected unexpected serious adverse reaction (SUSAR) refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP is suspected by either the sponsor or the investigator, is not listed in the applicable Reference Safety Information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. All individually reported SARs are considered suspected.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines.

Adverse Events of Special Interest

The following AESIs will be monitored during the study:

- Polyneuropathy
- Weight loss
- Hallucinations/psychosis
- Somnolence

Hallucinations, especially visual hallucinations, are a common symptom in patients with PD and could be associated with disease progression, comorbid pathologies, and/or concomitant medications. Older subjects, especially with history of hallucination and psychosis, are more at risk of exacerbating psychotic symptoms even if these are well controlled with antipsychotic medications at Baseline. Hallucinations might be prevented by managing psychogenic medications that might have been introduced during the parent study or while in the current study. Should hallucinations appear during this study, standard of care may be applied. This should include a conservative approach of assessing alternative etiologies and addressing them as appropriate and if none are found, waiting a few days to see if the phenomenon resolves spontaneously; the ultimate decision on how an individual subject is managed during the study, however, is the responsibility of the investigator or designee.

Local tolerability will be assessed. Infusion site evaluations will be performed at each scheduled clinic visit and may be performed at an unscheduled clinic visit. Any observation of infusion site irritation/reaction (> 2 or > C on the infusion site evaluation scale) must be recorded as an AE. Other infusion site-related reactions such as cellulitis/abscess formation, ecchymoses, subcutaneous nodules, or scarring should be evaluated and recorded as AEs. An independent review of moderate and severe infusion site-related reactions will be performed.

Adverse Event Severity and Relationship to Study Drug

Investigators will rate the severity of each AE as mild, moderate, or severe.

Investigators will use the following definitions to rate the severity of each AE:

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

The investigator will use the following definitions to assess the relationship of the AE to the use of the study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

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

Medical Complaints/Adverse Events and Serious Adverse Events: Study Medical Device

Adverse Event

An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours after the site is made aware of the SAE:

- Led to death, injury, or permanent impairment to a body structure of body function
- Led to a serious deterioration in the health of a subject that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - inpatient hospitalization or prolongation of existing hospitalization, or
  - medical or surgical intervention to prevent life threatening illness
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned hospitalization for a preexisting condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered an SAE.

Adverse Device Effects

Adverse device effects are AEs related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effects

Serious adverse device effects are adverse device effects that have resulted in any of the consequences characteristic of an SAE.

Device Deficiency

A device deficiency is an inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety, or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

If a device deficiency meets any of the following criteria, it is to be reported to AbbVie within 24 hours after the site is made aware:

- Any SAE
- Any device deficiency that may have led to a SAE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - circumstances had been less fortunate
- New findings/updates in relation to already reported events

Device Causality Assessment

The investigator will use the following definitions to assess the relationship of the reportable device event.

Not Related – Relationship to the device can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of a similar devices and procedures;
- the event has not temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g., and underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors);
- the event does not depend on a false result given by the investigational device use for diagnosis when applicable;
- harm to the subject are not clearly due to use error.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely – the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible – the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable – the relationship with the use of the investigational device seems relevant and/or the even cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship – the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partner(s) will be collected from the date of initiation of the infusion through 30 days after the end of the infusion.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the interim database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

Sample Size Estimation

Approximately 240 subjects will be enrolled to obtain exposure data from at least 100 subjects treated with 24-hour daily CSCI of ABBV-951 for at least 12 months and to meet country requirements. With 240 subjects receiving ABBV-951, the probability to observe an AE with an annual incidence rate of 0.005, 0.01, and 0.02 is 70%, 91%, and 99%, respectively.

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) consists of all subjects who receive at least 1 ABBV-951 infusion and have a baseline and treatment observation for at least 1 efficacy outcome measure. The Treatment-Naive Analysis Set (TNAS) consists of all subjects in the FAS who have the initial exposure to ABBV-951 in Study M15-741, i.e., subjects who had received ABBV-951 in another study prior to participating in Study M15-741 are excluded from the TNAS.

The Safety Analysis Set consists of all subjects who receive any ABBV-951 infusion.

All analyses will be conducted by dose subgroup (low dose or high dose) with a cutoff of 2800 mg LDP but could be revised based on an assessment conducted when 50 subjects reach Week 4 or the end of the Optimization Period. Each subject will be categorized to a dose subgroup based on the average total daily dose over the treatment period.

7.3 Statistical Analyses for Efficacy

This is a single-arm, open-label study. Unless stated otherwise, all analyses on efficacy variables will be performed with the FAS using data collected no more than 1 day after the end of the infusion of ABBV-951. An exploratory efficacy analysis of normalized daily "Off" time will be conducted on the TNAS. A paired-sample t-test will be performed for testing the change from Baseline.

For all efficacy endpoints, the change from Baseline to each planned visit and to the final visit will be summarized in a descriptive manner for each dose subgroup and overall subjects. The statistics include the number of observations, mean, standard deviation, minimum, median, and maximum.

7.4 Statistical Analyses for Safety

Safety analyses will be carried out using the Safety Analysis Set. Safety will be assessed by AEs, the Infusion Site Evaluation Scale, laboratory values, vital sign measures, ECGs, and safety scales including

the C-SSRS and Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS). All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment emergent AEs by MedDRA system organ class and preferred term, by severity, and by relationship to study treatment as assessed by the investigator will be provided for each dose subgroup and overall subjects. For continuous safety outcomes, the change from Baseline will be analyzed in a descriptive manner by visit for each dose subgroup and overall subjects. For categorical safety outcomes, the number and percentage of each category will be summarized by visit for each dose subgroup and overall subjects. Hypothesis testing will not be performed.

7.5 Interim Analysis

Two interim analyses will be performed during the course of this study. The first interim analysis will be performed after at least 100 subjects have completed 26 Weeks of therapy; the second interim analysis will be performed after at least 100 subjects have completed 52 Weeks of therapy.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

A subject may withdraw consent for optional biomarker samples at any time and remain in the clinical study. Data generated from optional biomarker samples before subject withdrawal of consent will be retained.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in 0.

In the event a significant disaster/crisis (including the COVID-19 pandemic) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit or date of the last follow-up contact, whichever is later.

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
aPD	advanced Parkinson's disease
AR	adverse reaction
CD	carbidopa
CD/LD	carbidopa/levodopa
CDP	carbidopa phosphate
CDP/LDP	carbidopa phosphate/levodopa phosphate
CLES	carbidopa-levodopa enteral suspension
COMT	catechol-*O*-methyltransferase
CR	controlled release
CSCI	continuous subcutaneous infusion
C-SSRS	Columbia-Suicide Severity Rating Scale
DDCI	DOPA decarboxylase inhibitor
DNA	deoxyribonucleic acid
DO	Doctor of Osteopathy
ECG	Electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5-dimensions questionnaire
EQ VAS	EQ visual analogue scale
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
ICD	impulse control disorder
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product

IR	immediate release
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IU	International Unit
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
LCIG	levodopa-carbidopa intestinal gel
LD	levodopa
LDP	levodopa phosphate
LED	levodopa equivalent dose
MAO	monoamine oxidase
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
M-EDL	Motor Aspects of Experiences of Daily Living
MMA	methylmalonic acid
MMSE	Mini-Mental State Examination
MW	molecular weight
nM-EDL	Non-Motor Aspects of Experiences of Daily Living
NP	Nurse Practitioner
PA	Physician's Assistant
PCS	potentially clinically significant
PD	Parkinson's disease
PDQ-39	PD Questionnaire-39 item
PDSS-2	PD Sleep Scale-2
PhD	Doctor of Philosophy
PKG	Parkinson's KinetiGraph™ or Personal KinetiGraph™ (United States)
PLMS	periodic leg movements of sleep
PRO	patient-reported outcome
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's correction formula
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBD	rapid eye movement behavior disorder
RLS	restless leg syndrome

RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
S.INF	solution for infusion
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	therapeutic area medical director
TN	treatment-naïve
TNAS	Treatment-Naïve Analysis Set
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VAS	visual analog scale
WOCBP	women of childbearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M15-741: A 52-Week, open-label, single-arm study to evaluate the safety and tolerability of 24-hour daily exposure of CSCI of ABBV-951 in subjects with Parkinson's disease

Protocol Date: 11 February 2021

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Group Medical Director	Neuroscience Development
	Medical Director	Neuroscience Development
	Assistant Scientific Director	Neuroscience Development
	Senior Director and Statistics TA Head	Data and Statistical Sciences
	Program Lead I	Clinical Program Development
	Study Project Manager II	Clinical Program Development
	Principal Medical Writer	Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

Required study activities are shown in the following table. Individual activities are described in detail in Section 3 of the Operations Manual (Appendix F).

Study Activities Table

Activity	Screening (V1)	Screening (V2)	Treatment Period: Optimization Period 4 Weeks: Enrollment Day 1 (V3)	Day 2 (V4)	Week 1 (V5)	Week 2 (V6)	Week 3 (V7)	Week 4 (V8)	Treatment Period: Maintenance Period 48 Weeks: Week 6 (V9)	Week 13 (V10)	Week 26 (V11)	Week 39 (V12)	Week 52 (V13)/ Premature Discontinuation	Post-study Completion/Premature Discontinuation Follow-up Call[d]	Dispensing Visits[c]
INTERVIEWS & QUESTIONNAIRES															
Subject information and informed consent	✓														
Eligibility criteria	✓	✓	✓ (predose)												
Medical history	✓														
Clinical assessment	✓														
Advanced Parkinson's Disease (aPD) Clinician Assessment	✓														
Infusion site evaluation (dermatologic assessment if applicable)			✓ (postdose)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Drug and alcohol screen	✓														
AE assessment	✓	✓	✓ (postdose)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Activity	Screening (V1)	Screening (V2)	Treatment Period: Optimization Period 4 Weeks: Enrollment Day 1 (V3)	Day 2 (V4)	Week 1 (V5)	Week 2 (V6)	Week 3 (V7)	Week 4 (V8)	Maintenance Period 48 Weeks: Week 6 (V9)	Week 13 (V10)	Week 26 (V11)	Week 39 (V12)	Week 52 (V13)/ Premature Discontinuation	Post-study Completion/Premature Discontinuation Follow-up Call[d]	Dispensing Visits[c]
Product complaints			✓ (pre- and postdose)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy	✓	✓	✓ (pre- and postdose)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Patient Reported Outcomes															
Patient Administered Measures (specific time points)															
Subject dosing diary					2 days before visit ✓	2 days before visit ✓	2 days before visit ✓	2 days before visit ✓	2 days before visit ✓	2 days before visit ✓	2 days before visit ✓	2 days before visit ✓	2 days before visit ✓		
Parkinson's Disease Diary	✓ (concor-dance evalu-ation)		2 days before visit ✓		2 days before visit ✓				2 days before visit ✓		2 days before visit ✓	2 days before visit ✓	2 days before visit ✓		
PKG wearable device	✓[a]	✓[a]	✓[a]	✓	✓	✓	✓	✓	✓	✓	✓	optional	optional		
EQ-5D-5L			✓ (predose)						✓	✓	✓	✓	✓		
Rater Administered Measures (specific time points)															
C-SSRS	✓	✓	✓ (predose)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
PDQ-39			✓ (predose)						✓	✓	✓	✓	✓		

Activity	Screening (V1)	Screening (V2)	Treatment Period: Optimization Period 4 Weeks: Enrollment Day 1 (V3)	Day 2 (V4)	Week 1 (V5)	Week 2 (V6)	Week 3 (V7)	Week 4 (V8)	Maintenance Period 48 Weeks: Week 6 (V9)	Week 13 (V10)	Week 26 (V11)	Week 39 (V12)	Week 52 (V13)/ Premature Discontinuation	Post-study Completion/Premature Discontinuation Follow-up Call[d]	Dispensing Visits[c]
MDS-UPDRS/UPDRS	✓		✓ (pre- and postdose)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
PDSS-2			✓ (predose)						✓	✓	✓	✓	✓		
MMSE	✓														
QUIP-RS			✓ (predose)						✓	✓	✓	✓	✓		
LABS & EXAMS															
Clinical laboratory tests	✓		✓ (predose)						✓		✓	✓	✓		
Special laboratory tests (vitamins B_6 and B_{12}, folic acid, MMA, homocysteine)	✓		✓ (predose)						✓		✓		✓		
Optional biomarker samples (pharmacogenetic DNA)			✓ (predose)								✓				
12-lead ECG	✓		✓ (postdose)						✓				✓		
Height (V1 only) and weight	✓		✓ (predose)						✓		✓		✓		
Orthostatic vital signs			✓ (postdose)		✓				✓		✓		✓		
Vital signs	✓	✓		✓		✓	✓	✓		✓		✓			

Activity	Screening (V1)	Screening (V2)	Treatment Period: Optimization Period 4 Weeks: Enrollment Day 1 (V3)	Day 2 (V4)	Week 1 (V5)	Week 2 (V6)	Week 3 (V7)	Week 4 (V8)	Maintenance Period 48 Weeks: Week 6 (V9)	Week 13 (V10)	Week 26 (V11)	Week 39 (V12)	Week 52 (V13)/ Premature Discontinuation	Post-study Completion/Premature Discontinuation Follow-up Call[d]	Dispensing Visits[c]
Physical exam	✓		✓ (predose)						✓		✓		✓		
Neurological exam	✓		✓ (predose)						✓	✓	✓	✓	✓		
Serum pregnancy test at central lab	✓														
Local urine pregnancy test[b]			✓ (predose)										✓		
℞ TREATMENT															
Drug delivery system training		✓	✓												
Study drug infusion			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Verify supply of drug, investigational devices and ancillaries			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Verify reconciliation of drug and investigational devices			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Dispense/return drug delivery system			Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51. Used and unused vials dispensed at the previous visit should be returned by the subject (before dispensing new vials) at Week 1 and every 2 weeks thereafter; all drug delivery components should be returned by the subject at Week 52/premature discontinuation.												
Study drug prescription record			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			

a. As allowed by local regulations, the PKG watch will be given to the subject following V1, after being received by the study site, and prior to the monitoring period. The 6-day Monitoring Period can occur any time before V3 once the PKG watch has been received by the study site, lasting for a minimum of 6 consecutive days. PD Diaries will also be

collected for at least 2 consecutive days during the same 6-day Monitoring Period. In countries where the PKG watch is not approved, the Monitoring Period may be reduced to at least 2 days to account for the collection of PD Diaries and pump training.

b. Urine pregnancy tests will be performed monthly for women of childbearing potential. If there is a scheduled visit, the test will be performed on site; if there is not a scheduled visit, the test may be performed at an unscheduled visit or at home.

c. Dispensing visits may occur with or without a clinic visit being completed.

d. If the subject is willing, the post-study completion/premature discontinuation follow-up call will occur 30 days after premature discontinuation from the study or 30 days after completion of Week 52 for subjects not enrolling in the extension study.

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	17 July 2018
Version 2.0	15 November 2018
Version 3.0	11 February 2019
Version 3.1 (United States and Japan)	18 April 2019
Version 3.1.1 (United States and Japan)	26 April 2019
Version 4.0	28 August 2019
Version 4.1 (Germany only)	02 January 2020
Version 5.0	02 March 2020
Version 6.0	09 April 2020
Version 6.1 (Sweden only)	11 June 2020
Version 6.2 (Germany only)	11 June 2020
Version 6.1.1 (Sweden only)	08 September 2020
Version 6.1.1.1 (Sweden only)	20 November 2020

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol and incorporate necessary protocol modifications due to the COVID-19 pandemic, as well as other changes as follows:

1. Sample size estimation was updated to approximately 240 subjects to accommodate participation of additional countries, to account for the higher-than-expected dropout rate and to gain additional safety data.
2. Clarified that F3 infusion rate may be reduced beyond the 20% limit from the prescribed base infusion rate (F1) if medically necessary and only with approval from the AbbVie TA MD.
3. Included information on the re-evaluation of the benefit and risk to subjects participating in the study to reflect that there is no additional risk to subjects due to COVID-19 (Protocol Section 2.2).
4. Modified/added eligibility criteria to minimize additional risk to study subjects or exclude subjects positive for COVID-19 (Protocol Section 5.1).
5. Clarified that protocol deviations may include modifications due to COVID-19 (Protocol Section 5.9)
6. Added instructions for COVID-19 pandemic-related acceptable protocol modifications and to refer to the Operations Manual for details on how to handle necessary changes to activities or procedures (Protocol Section 4.1 and Section 5.5).

7. Noted that AbbVie will modify the study protocol as necessary due to the COVID-19 pandemic. Investigators must also notify AbbVie if any urgent safety measures are taken (Protocol Section 8.2).
8. Noted that remote monitoring during the COVID-19 pandemic may be employed as needed (Protocol Section 9).
9. Operations Manual (Appendix F) updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the COVID-19 pandemic.
10. Added additional details regarding ABBV-951 and infusion site reactions (Protocol Section 4.1).

    Rationale: *To provide further guidance to Investigators in the event of an infusion site reaction.*
11. Added hallucinations/psychosis as a common symptom in patients with PD and included general guidance (Protocol Section 6.1).

    Rationale: *To provide general guidance to investigators on possible causes of hallucinations/psychosis in the study population and management approaches that can be considered.*
12. Added text to clarify that the appropriate cannula length will be selected by the investigator based on individual subject characteristics (thickness of the abdominal subcutaneous fat tissue) and noted that the investigator should consider instructing the subject to rotate the infusion site more frequently (Protocol Section 5.8).

    Rationale: *To mitigate the risk of muscle wall infiltration leading to pain and/or occlusion of the cannula and to prevent overuse of an infusion site area.*
13. Added alternative infusion site locations and considerations guidance (Protocol Section 5.8).
14. Removed references to "caregivers" throughout protocol and Operations Manual.
15. Changed the reporting timeframe for product complaints to 24 hours (Protocol Section 6.1).

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M15-741

Parkinson's Disease: Safety and Tolerability of 24-Hour Daily Exposure to ABBV-951 by Continuous Subcutaneous Infusion

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-951

FULL TITLE: A 52-Week, open-label, single-arm study to evaluate the safety and tolerability of 24-hour daily exposure of continuous subcutaneous infusion of ABBV-951 in subjects with Parkinson's disease

1 CONTACTS

Sponsor/ Emergency Medical Contact	**Sponsor Contact:** [redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Office: Mobile: Fax: Email: [redacted]
	Emergency Medical Contact: [redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Office: Mobile: Fax: Email: [redacted] **EMERGENCY 24-hour Number:** **+1 973-784-6402**
Safety Concerns	**Neuroscience Safety Team** AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 847-938-4191 Email: SafetyManagement_Neuroscience@abbvie.com
SAE Reporting outside of RAVE	**Clinical Pharmacovigilance**	Fax: +1 847-938-0660 Email: PPDINDPharmacovigilance@abbvie.com
Protocol Deviations	[redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: Email: [redacted]
Certified Clinical Laboratory	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214	Phone: +1 866-762-6209 (toll free) +1 317-271-1200 (local calls) Fax: +1 317-616-2361
Biomarker Sample Laboratory	Pharmacogenetics and Pharmacogenomics [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 847-938-8525

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LIST OF APPENDICES

2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as remote visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the guidance below on how to proceed.

If a subject has screened and is unable to complete screening activities on site after Screening Visit 1, the Screening Period should be extended as described in Protocol Section 4.1 rather than performing remote Visit 2, since Day 1 and Day 2 visits are required to be completed onsite. The guidance that is provided for Week 1 visit and beyond should be followed if the COVID-19 restrictions at your site have changed once your subject is enrolled.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, study visits for Weeks 1, 2, 3, 4, 6, 13, and 39 may be conducted remotely. The Enrollment Visit (Day 1), Day 2 visit, Week 26 visit, and the Final Week 52/Premature Discontinuation visit are required to be completed onsite. It is highly recommended that all visits during the Optimization Period (Weeks 1, 2, 3 and 4 visits) be conducted onsite whenever possible.
- Some study visits and/or activities may be performed by phone/remotely. These are indicated by a hashtag (#) in the appropriate visit tables below.
- During a phone/remote visit, activities that do not need to be performed are indicated by a minus sign (–).
- Scheduled and unscheduled labs may be drawn by a local clinic/hospital/laboratory if COVID-19 restrictions prevent a subject to visit the site. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed:
    - For Week 26 and Week 52, if the visit cannot be rescheduled within the visit window, contact the sponsor. Subjects should remain on study drug as much as possible through Week 52/Premature Discontinuation.

If an activity is missed during a remote visit, perform the activity at the earliest feasible opportunity. Laboratory draws must be obtained as soon as feasible.

2.1 Screening Period Activities

A list of activities is presented in this section. Activities are grouped by category (Interview, Exam, etc.). Details about each activity are provided in Section 3.

SCREENING VISIT 1 (V1):

INTERVIEW	• Subject information and informed consent • Evaluation of eligibility criteria • Medical history • Clinical assessment	• Advanced Parkinson's disease (aPD) clinician assessment • Drug and alcohol screen • Adverse event (AE) assessment • Prior/concomitant therapy assessment
PATIENT REPORTED OUTCOME (PRO)	• Parkinson's disease (PD) diary training and concordance evaluation[a] • Columbia-Suicide Severity Rating Scale (C-SSRS)	• Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)/UPDRS • Mini-Mental State Examination (MMSE) • Provide Parkinson's KinetiGraph (PKG) to subject following V1 and prior to the Monitoring Period[b] (in countries where allowed and once received by study site)
EXAM	• 12-lead electrocardiogram (ECG) • Height and weight	• Vital signs • Physical/neurological exam
LAB	• Clinical laboratory tests (central lab) • Special laboratory tests (central lab)	• Serum pregnancy test (central lab)

a. The concordance test may be omitted for subjects previously enrolled in Study M15-739, for whom recognizable/identifiable "Off" and "On" state (motor fluctuations) have been already established and confirmed. The concordance test may also be omitted for subjects for whom recognizable/identifiable "Off" and "On" state (motor fluctuations) have been already established and confirmed, and for unforeseen circumstances, require rescreening.

b. The 6-day Monitoring Period can occur any time before V3 once the PKG watch has been received by the study site, lasting for a minimum of 6 consecutive days. PD Diaries will also be collected for at least 2 consecutive days during the same 6-day Monitoring Period. In countries where the PKG watch is not approved, the Monitoring Period may be reduced to at least 2 days to account for the collection of PD Diaries and pump training.

Note: Screening Visit 1 is required to be performed onsite.

SCREENING VISIT 2 (V2):

INTERVIEW	• Evaluation of eligibility criteria • AE assessment	• Prior/concomitant therapy assessment
PRO	• C-SSRS	
EXAM	• Vital signs	
TREATMENT	• Drug delivery system training	

Note: Screening Visit 2 is required to be performed onsite.

MONITORING PERIOD:

INTERVIEW	• Wear PKG for at least 6 consecutive days any time prior to V3 (in countries where allowed)	• PD diary (2 consecutive days while wearing PKG prior to V3, site phone call reminder)

2.2 Treatment Period Activities

A list of activities performed during each visit, organized by visit, is presented in this section. The dot pattern on the upper right indicates the place of the visit in the Treatment Period. Activities are grouped by category (Interview, Exam, etc.). Details about each activity are provided in Section 3. Unscheduled clinic visits may occur per investigator discretion as deemed necessary. The appropriate protocol assessments to be conducted at an unscheduled visit are to be determined by the investigator.

ENROLLMENT/DAY 1 (V3):

INTERVIEW	• Evaluation of eligibility criteria[a] • Infusion site evaluation (dermatologic assessment if applicable)[b] • AE assessment[b]	• Product complaints[a,b] • Prior/concomitant therapy assessment[a,b]
PRO	• PD diary (2 consecutive days before visit, site phone call reminder) • EQ-5D-5L[a] • C-SSRS[a] • PDQ-39[a] • MDS-UPDRS/UPDRS ("Off"[a] and "On"[b])	• PDSS-2[a] • Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)[a] • Wear PKG
EXAM	• 12-lead ECG[b] • Weight[a]	• Orthostatic vital signs[b] • Physical/neurological exam[a]
LAB	• Clinical laboratory tests (central lab)[a] • Special laboratory tests (central lab)[a]	• Optional biomarker sample for pharmacogenetics (PG-DNA)[a] • Urine pregnancy test (locally with test provided by central lab)[a,c]
TREATMENT	• Drug delivery system training • Start study drug infusion • Verify supply of study drug, investigational devices, and ancillaries • Verify reconciliation of drug and investigational devices	• Dispense drug delivery system[d] • Study drug prescription record

EQ-5D-5L = EuroQol 5-dimensions questionnaire; PDQ-39 = Parkinson's Disease Questionnaire-39 item; PDSS-2 = Parkinson's Disease Sleep Scale-2

a. Before ABBV-951 initiation.

b. After ABBV-951 initiation.

c. A urine pregnancy test for women of childbearing potential will be performed prior to the initiation of the CSCI of ABBV-951 on Day 1 (V3) then monthly thereafter during the Treatment Period as well as at the end of treatment (Week 52 [V13]) or at premature discontinuation. If there is a scheduled visit, the test will be performed on site; if there is not a scheduled visit, the test may by performed at an unscheduled visit or at home.

d. Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51.

Note: The Enrollment/Day 1 (V3) is required to be performed onsite.

DAY 2 (V4):

INTERVIEW	• Infusion site evaluation (dermatologic assessment if applicable) • AE assessment	• Product complaints • Prior/concomitant therapy assessment
PRO	• C-SSRS	• MDS-UPDRS/UPDRS • Confirm wearing of PKG
EXAM	• Vital signs	
TREATMENT	• Study drug infusion • Verify supply of drug, investigational devices, and ancillaries	• Verify reconciliation of drug and investigational devices • Study drug prescription record

Note: The Day 2 visit is required to be performed onsite.

WEEK 1 (V5):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• # Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • PD diary (2 consecutive days before visit, site phone call reminder)	• # C-SSRS • # MDS-UPDRS/UPDRS • # Confirm wearing of PKG
EXAM	• – Orthostatic vital signs	
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • Dispense/return drug delivery system[a] • # Study drug prescription record[b]

a. Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51. Used and unused vials dispensed at the previous visit should be returned by the subject (before dispensing new vials) at Week 1 and every 2 weeks thereafter; all drug delivery components should be returned by the subject at Week 52/premature discontinuation.

b. The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

– These activities do not need to be performed during virtual visits.

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 2 (V6):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• # Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • # C-SSRS	• # MDS-UPDRS/UPDRS • # Confirm wearing of PKG
EXAM	• – Vital signs	
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • # Study drug prescription record[a]

The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

\# These activities may be performed remotely.

– These activities do not need to be performed during virtual visits.

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 3 (V7):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• # Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • # C-SSRS	• # MDS-UPDRS/UPDRS • # Confirm wearing of PKG
EXAM	• – Vital signs	
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • Dispense/return drug delivery system[a] • # Study drug prescription record[b]

a. Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51. Used and unused vials dispensed at the previous visit should be returned by the subject (before dispensing new vials) at Week 1 and every 2 weeks thereafter; all drug delivery components should be returned by the subject at Week 52/premature discontinuation.

b. The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

These activities may be performed remotely.

– These activities do not need to be performed during virtual visits.

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 4 (V8):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• # Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • # C-SSRS	• # MDS-UPDRS/UPDRS • # Confirm wearing of PKG
EXAM	• – Vital signs	
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • # Study drug prescription record[a]

a. The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

These activities may be performed remotely.

– These activities do not need to be performed during virtual visits.

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 6 (V9):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• # Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • PD diary (2 consecutive days before visit, site phone call reminder) • # EQ-5D-5L	• # C-SSRS • # PDQ-39 • # MDS-UPDRS/UPDRS • # PDSS-2 • # QUIP-RS • # Confirm wearing of PKG
EXAM	• – 12-lead ECG • – Weight	• – Orthostatic vital signs • – Physical/neurological exam
LAB	• Clinical laboratory tests (central lab)	• Special laboratory tests (central lab)
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • # Study drug prescription record[a]

a. The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

These activities may be performed remotely.

– These activities do not need to be performed during virtual visits

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 13 (V10):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • # EQ-5D-5L • # C-SSRS • # PDQ-39	• # MDS-UPDRS/UPDRS • # PDSS-2 • # QUIP-RS • # Confirm wearing of PKG
EXAM	• – Vital signs	• – Neurological exam
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • Dispense/return drug delivery system[a] • # Study drug prescription record[b]

a. Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51. Used and unused vials dispensed at the previous visit should be returned by the subject (before dispensing new vials) at Week 1 and every 2 weeks thereafter; all drug delivery components should be returned by the subject at Week 52/premature discontinuation.

b. The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

These activities may be performed remotely.

– These activities do not need to be performed during virtual visits.

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 26 (V11):

INTERVIEW	• Infusion site evaluation (dermatologic assessment if applicable) • AE assessment • Product complaints	• Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • PD diary (2 consecutive days before visit, site phone call reminder) • EQ-5D-5L	• C-SSRS • PDQ-39 • MDS-UPDRS/UPDRS • PDSS-2 • QUIP-RS • Confirm wearing of PKG
EXAM	• Weight • Physical/neurological exam	• Orthostatic vital signs
LAB	• Clinical laboratory tests (central lab) • Special laboratory tests (central lab)	• Optional biomarker sample for pharmacogenetics (PG-DNA)
TREATMENT	• Study drug infusion • Verify supply of drug, investigational devices, and ancillaries	• Verify reconciliation of drug and investigational devices • Study drug prescription record

Note: The Week 26 visit (V11) is required to be performed onsite.

WEEK 39 (V12):

INTERVIEW	• # Infusion site evaluation (dermatologic assessment if applicable) • # AE assessment • # Product complaints	• Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • PD diary (2 consecutive days before visit, site phone call reminder) • # EQ-5D-5L	• # C-SSRS • # PDQ-39 • # MDS-UPDRS/UPDRS • # PDSS-2 • # QUIP-RS • # Confirm wearing of PKG (optional)
EXAM	• – Vital signs	• – Neurological exam
LAB	• - Clinical laboratory tests (central lab)	
TREATMENT	• # Study drug infusion • # Verify supply of drug, investigational devices, and ancillaries	• # Verify reconciliation of drug and investigational devices • Dispense/return drug delivery system[a] • # Study drug prescription record[b]

a. Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51. Used and unused vials dispensed at the previous visit should be returned by the subject (before dispensing new vials) at Week 1 and every 2 weeks thereafter; all drug delivery components should be returned by the subject at Week 52/premature discontinuation.

b. The study drug prescription record cannot be changed remotely; however, if the visit is performed remotely, the values for the study drug prescription record should be recorded in EDC as specified in the Data Entry Guide.

These activities may be performed remotely.

– These activities do not need to be performed during virtual visits.

Note: The MDS-UPDRS Part III (Motor Examination) cannot be performed remotely. For guidance related to remote assessment of the MDS-UPDRS, please see Operations Manual Section 3.10.

WEEK 52 (V13) OR PREMATURE DISCONTINUATION:

INTERVIEW	• Infusion site evaluation (dermatologic assessment if applicable) • AE assessment • Product complaints	• Prior/concomitant therapy assessment
PRO	• Subject dosing diary (2 consecutive days before visit, site phone call reminder) • PD diary (2 consecutive days before visit, site phone call reminder) • EQ-5D-5L	• C-SSRS • PDQ-39 • MDS-UPDRS/UPDRS • PDSS-2 • QUIP-RS • Confirm wearing of PKG (optional)
EXAM	• 12-lead ECG • Weight	• Orthostatic vital signs • Physical/neurological exam
LAB	• Clinical laboratory tests (Central lab) • Special laboratory tests (central lab)	• Urine pregnancy test (locally with test provided by central lab)
TREATMENT	• Verify reconciliation of drug and investigational devices	• Return drug delivery system

Notes: Subjects who prematurely discontinue participation or are not enrolled in the extension study (Study M15-737) will receive a telephone call from study site staff 30 days after the end of the infusion of study drug if the subject is willing.

The Week 52 or Premature Discontinuation Visit are required to be performed onsite.

POST-STUDY COMPLETION/PREMATURE DISCONTINUATION FOLLOW-UP CALL:

INTERVIEW	• AE assessment

DISPENSING VISITS

TREATMENT	• Verify supply of study drug, investigational devices, and ancillaries	• Verify reconciliation of drug and investigational devices • Dispense/return drug delivery system[a]

a. Investigational product will be dispensed on Day 1, at Week 1, and every 2 weeks thereafter through Week 51. Used and unused vials dispensed at the previous visit should be returned by the subject (before dispensing new vials) at Week 1 and every 2 weeks thereafter; all drug delivery components should be returned by the subject at Week 52/premature discontinuation.

2.3 Post-Treatment Activities

Subjects who prematurely discontinue the study or are not enrolled in the extension study (Study M15-737) will receive a 30-day follow-up call after the end of infusion of study drug, if the subject is willing. See Protocol Section 5.7 for additional information.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and the investigator will answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Samples for optional biomarker analyses will only be collected if the subject has voluntarily signed and dated a separate written consent form for optional biomarker testing that has been approved by an institutional review board/independent ethics committee (IRB/IEC), after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form, according to local regulations. If the subject does not consent to the optional biomarker samples, it will not impact the subject's participation in the study.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not stated in this protocol and/or Operations Manual may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or

substantial changes in study conduct in accordance with local regulations. The subject's source documentation should indicate that verbal consent was obtained.

Informed consent will be obtained at Screening Visit 1 (V1) as shown in Section 2.

3.2 Eligibility Criteria

All subjects will be evaluated to ensure they meet the eligibility criteria at Screening Visits 1 and 2 (V1 and V2) and prior to enrollment on Day 1 (V3) as shown in Section 2.

3.3 Medical History

A complete medical history, including demographics and histories of alcohol or drug abuse, that in the investigator's judgment might impact compliance with study execution, will be taken at Screening Visit 1 (V1) as shown in Section 2. Additionally, chronic disorders (e.g., diabetes, hypertension, hay fever, polyneuropathy) that began prior to Screening Visit 1 (V1) and are still present at Screening Visit 1 (V1) should be recorded on the Medical History Form. The medical history obtained at Screening Visit 1 (V1) will serve as the Baseline for clinical assessment. All psychiatric, neurological, behavioral, and/or cognitive diagnoses should be reported. Updates should be made to the medical/neurological/PD history with any findings from laboratories, dermatologists, etc. related to the period before initiation of study drug. Medication (prescription or over-the-counter, including vitamins and herbal supplements) use from 30 days prior to informed consent form signature through the end of the study will also be recorded.

3.4 Clinical Assessments

A clinical assessment will be conducted on all subjects at Screening Visit 1 (V1) as shown in Section 2. This will include an assessment of the subject's PD treatment history, including the Advanced Parkinson's Disease (aPD) Clinician Assessment.[1] To qualify for enrollment in the study, the subject should provide the investigator with a comprehensive history of their current and past (possibly up to 5 years) PD medication. This should be done according to the subject's recollection, as well as available history in a subject's chart.

The investigator or qualified designee will complete the aPD Clinician Assessment to determine if the subject has inadequate control of their motor symptoms despite treatment with PD medications and therefore requires advanced PD treatment.

3.5 Study Drug Prescription Record

Starting on Day 1 (V3) through the end of the study as shown in Section 2, the subject's pump settings (continuous infusion rate in mL/hr and extra dose volume in mL) should be recorded at the conclusion of each visit on the study drug prescription record.

3.6 Infusion Site Evaluation

The investigator or qualified designee will evaluate the infusion site area (abdomen) from Day 1 (V3) through the end of the study, as shown in Section 2.

At the time of each evaluation, the following rating scales will be used:[2]

Irritation – Numeric Grades
0 = No evidence of irritation
1 = Minimal erythema, barely perceptible
2 = Moderate erythema, readily visible; or minimal edema; or minimal papular response
3 = Erythema and papules
4 = Definite edema
5 = Erythema, edema, and papules
6 = Vesicular eruption
7 = Strong reaction spreading beyond the test site

Irritation – Letter Grades
A = No finding
B = Slight glazed appearance
C = Marked glazing
D = Glazing with peeling and cracking
E = Glazing with fissures
F = Film of dried serous exudates covering all or portion of the patch site
G = Small petechial erosions and/or scabs

Any observation of infusion site reaction with irritation criteria > 2 or > C must be recorded as an adverse event (AE).

Dermatologic Assessment

If any moderate to severe infusion site related AE, such as cellulitis/abscess formation, ecchymoses, subcutaneous nodules, or scarring occurs, or if any infusion site related reaction is assessed with an irritation numeric grade equal to 7 on the Infusion Site Evaluation scale, the investigator or designee is instructed to do the following, which will be documented in the eCRF:

1. Photograph the skin reaction and follow the appropriate procedure for submission of photographs. In rare situations where an assessment or visit cannot be completed onsite due to an extenuating event (e.g., COVID-19-related conditions), the subject may be asked to obtain and submit a self-captured photograph of the skin reaction.
2. Refer the subject to a dermatologist for comprehensive evaluation (including skin biopsy, if applicable), treatment, and follow-up per standard practice. The subject should be referred to a dermatologist within 2 business days after the photographs are taken. The dermatologic visit should be completed within 2 weeks from identification of the AE or skin reaction that meets the above criteria. While an in-person dermatology evaluation is preferred, this assessment may be performed as a telemedicine visit per the dermatologist's standard practice.

Photography data will be considered source documentation. Dermatologic assessments may be performed during clinic visits (scheduled or unscheduled).

Sites will request medical records from the dermatologic visit. Upon receipt of records or reports generated from the dermatologic visit, sites will promptly submit them to AbbVie or designee consistent with typical study data reporting requirements.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, the Infusion Site Evaluation (ISE) may be completed remotely via video conference at the study visits specified in Section 2 (provided the video is of sufficient quality). If the ISE is completed via video conference, the subject will be asked to describe the reaction (swelling, redness, etc.). Further, if the ISE meets the criteria for dermatologic assessment, request that a photo of the reaction be provided to the site in accordance with local regulations. AEs should be reported per protocol.

3.7 Drug and Alcohol Screen

Subjects should have no history of clinically significant drug or alcohol abuse within the last 6 months that can preclude adherence to the protocol, in the opinion of the investigator.

Urine specimens will be tested at Screening Visit 1 (V1) as shown in Section 2 for the presence of drugs of abuse and for alcohol. The panel for drugs of abuse will minimally include the drugs listed below. These analyses will be performed by the site or by the certified central laboratory. If the screen is performed by the site, test kits and the confirmation of positive results will be provided by the central laboratory. A positive confirmation will result in the subject's exclusion from the study only if in the opinion of the investigator, the subject's history of drug abuse could preclude adherence to the protocol. Similarly, if there is documented proof that the detected drug is appropriately prescribed by a physician, the subject might be enrolled in the study.

- Cannabinoids
- Opiates
- Barbiturates
- Amphetamines*
- Cocaine
- Benzodiazepines

* *A positive confirmation of amphetamine use, even if appropriately prescribed by a physician, will result in the subject's exclusion from enrollment in the study, as amphetamines are dopamine depleting agents and therefore prohibited in this study.*

3.8 Adverse Event Assessment

AEs will be assessed at every visit throughout the study as shown in Section 2. The investigator will routinely monitor each subject for clinical and laboratory evidence of AEs throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken.

For serious adverse events (SAEs) considered as having "no reasonable possibility" of being associated with study drug or the study device components, the investigator will provide an "other" cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by clinical study personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

See also Section 4.1.

3.9 Prior and Concomitant Medications

Investigators and/or trained site staff will review and record all prior and concomitant medications at every visit throughout the study as shown in Section 2.

3.10 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instruments. Subjects should be instructed to follow the instructions provided with the PRO instrument and to provide the best possible response to each item. Clinical study personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Clinical study personnel will encourage completion of the PRO instrument at all specified visits and will ensure that a response is entered for all items.

Subjects will also complete rater-administered PRO instruments, such as the Columbia-Suicide Severity Rating Scale (C-SSRS), the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS), and other assessments. All applicable clinical, safety, health outcome, and cognition assessments will be administered only by individuals qualified by the sponsor. Every effort must be made by the investigative sites to ensure that each subject is rated by the same rater throughout the subject's participation in the study.

Prior to administration of respective scale(s), designated raters will be trained on and certified (if appropriate) in the use of all the scales used in this study. The objective of this certification/training is to ensure uniformity across sites in the administration and scoring of these assessments.

The sponsor, in conjunction with the selected rater training vendor, if applicable, will determine the minimum rater qualifications for each of the rating scales. All raters must meet these qualifications prior to participation in the training process. The names and qualifications of all clinical study personnel to be involved in rating scale administration will be submitted for approval upon site selection. The qualifications of the raters will be verified through the training vendor. Qualified raters will be trained and tested for competency and, if they meet established requirements, certified accordingly. Individual exceptions to these requirements must be approved by the sponsor via the rater training vendor if applicable.

Only those persons who have been trained as raters for this study may rate subjects. Raters who cannot participate in the initial pre-study training or who become involved in the study at a later time will not be permitted to perform study ratings until they have satisfactorily completed an individualized training

program designed by the rater training vendor if applicable, approved by AbbVie, and supervised by the investigator or his/her designee. Raters may be reassessed periodically throughout the study.

The PRO assessments are described below. COVID-19 pandemic-related acceptable protocol modifications are described at the end of this section.

SLATE Device PRO (i.e., rater tablet): The preferred method is to collect data using direct entry into the SLATE device, even when collected remotely. Paper PROs may be used in certain cases; please discuss with the sponsor. Specifications are outlined below.

Site rater-administered scales via SLATE Device PRO: This includes MDS-UPDRS, C-SSRS, QUIP-RS, EQ-5D-5L, and PDQ-39, as applicable for each visit. The qualified rater at the site can conduct those assessments remotely as specified by protocol except for the MMSE and MDS-UPDRS Part III (Motor Examination). As default, the system does not allow raters to jump to the MDS-UPDRS Part IV without having completed Part III. In this case, "Unable to Rate" is the response choice on the MDS-UPDRS Part III that should be used to skip through the questions.

Paper versions of certain scales may be available for remote administration. Please discuss with the sponsor.

- Source documentation should clearly indicate how each scale was obtained (e.g., in-person, phone, video conference) with time/date noted for each scale and with rater's initials. Study personnel will transfer paper documentation to TrialManager (via SLATE device [i.e., rater tablet]) per instructions provided to the study site.

Subject Dosing Diary

Subjects will complete a dosing diary. The time a new syringe dose is started, changes in the preset pump flow rate, self-administered extra dose times, stoppage in therapy (e.g., vial change-out, shower), replacement of infusion sets, pump errors (e.g., occlusion alarm), and LD+DDCI tablets or levodopa inhalation powder self-administered by the subject during the study as possible rescue therapy should be recorded for 2 consecutive days prior to any study visits (as specified in Section 2). Additionally, all instances of the use of rescue therapy, change in pump flow rates, and self-administered extra doses should be documented in the dosing diary throughout the study. Completed dosing diaries should be submitted to the investigator at the first available occasion.

PD Diary

PD Diary Subject Training and Screening Requirements

The subject will be required to have PD Diary training that will include how to understand their PD symptomatology and how to complete the PD Diary. Training will occur during Screening Visit 1 (V1).

Completion of the PD Diary

The core of the PD Diary is the questionnaire that the subject will use to record Parkinsonian symptoms. The subject will be prompted to record in the PD Diary whether he/she has been "On," "Off," or "Asleep" and what the severity of his/her dyskinesia (troublesome or not troublesome) was. The PD Diary is to be completed for a full 24 hours of each day, reflecting both time awake and time asleep. On PD Diary recording days, the subject will be instructed to make an entry upon waking and every 30 minutes during their normal waking time and upon awakening from time asleep.

The PD Diary will be completed on 2 consecutive days prior to Day 1 (V3) during the Monitoring Period, and for 2 consecutive days immediately prior to the visits specified in Section 2. Subjects should be reminded with a phone call prior to each visit to complete the PD Diary and to reinforce the importance of PD Diary completion. If during the study, the subject incorrectly completes the PD Diary, they should receive re-training on PD Diary completion.

*PD Diary Concord*ance Assessment
Following the initial PD Diary training during Screening Visit 1 (V1), the subject will complete a PD Diary over a minimum of 3 hours for a concordance evaluation while he/she is in the clinic at Screening Visit 1 (V1) as shown in Section 2. During this period, the subject must experience at least 1 transition from "Off" to "On" or from "On" to "Off," which must be observed by the investigator or a qualified rater. The investigator or an experienced and medically qualified study site designee (e.g., NP, PA, DO, MD, or PhD) assigned by the investigator will also complete a separate PD Diary for this period indicating their assessment of the subject's motor state. There must be at least 75% concordance between the subject's PD Diary and the PD Diary completed by the investigator or qualified designee. If no transition from "Off" to "On" or from "On" to "Off" occurs during the time of concordance evaluation and/or the concordance is lower than 75%, the concordance testing may be prolonged at the discretion of the investigator or designee. If the concordance is less than 75%, the subject will undergo re-training of PD Diary completion and repeat the concordance evaluation at Screening Visit 2 (V2). Subjects previously enrolled in Study M15-739, for whom recognizable/identifiable "Off" and "On" state (motor fluctuations) have been already established and confirmed do not need to complete the concordance test. The PD diary concordance test may also be omitted for subjects for whom recognizable/identifiable "Off" and "On" state (motor fluctuations) have been already established and confirmed, and for unforeseen circumstances, require rescreening.

EuroQol 5-Dimension Questionnaire
The EuroQol 5-dimension questionnaire (EQ-5D-5L) is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Impairment in each of the 5 dimensions is measured on a 5-level scale, where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. The patient is asked to rate his/her current health by ticking the box next to the statement that most appropriately describes their health status in each of the 5 dimensions. The patient's overall health can be described as a single number (formed by the combination of the levels of impairment across each of the 5 dimensions) that ranges from 11111 (full health/ no problems) to 55555 (extreme impairment in all dimensions). The health status is converted to an index value using a country-specific weighted scoring algorithm. The index value for the United States (US) ranges from a worst score of –0.109 to a best score of 1.

In addition, the patient is also asked to self-rate their current health on a vertical visual analogue scale (VAS). The scale ranges from 0 (labelled as "the worst health you can imagine") to 100 (labelled as "the best health you can imagine"). The VAS provides a complementary approach to the descriptive system for quantifying the patient's health based on their own judgment.

Subjects will complete the EQ-5D-5L at the study visits specified in Section 2.

Columbia-Suicide Severity Rating Scale

The C-SSRS is a systematically administered instrument designed to assess suicidal behavior and ideation, track and assess all suicidal events, and assess the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents.

Answering "yes" to question 4 and/or question 5 of the suicidal ideation portion of the C-SSRS relative to the previous year, or to any category of the suicidal behavior portion of the C-SSRS relative to the last 2 years, is considered as an indicator of high risk for suicide and subjects will need to be evaluated immediately by the investigator. Similarly, if subjects express suicidal ideation or suicidal behavior at any time during the study, the investigator must evaluate the subjects immediately and consider whether they remain suitable for participation in the study. The AbbVie therapeutic area medical director (TA MD) should be notified immediately.

Under no circumstances should a subject who has positively endorsed or expressed suicidal ideation be left alone, be allowed to exit the site, or go home before a qualified medical professional has evaluated the subject's risk.

A qualified rater will administer the C-SSRS at the visits specified in Section 2. The C-SSRS will be administered prior to initiation of the continuous subcutaneous infusion (CSCI) of ABBV-951 on Day 1 (V3).

Parkinson's Disease Questionnaire

The Parkinson's Disease Questionnaire (PDQ-39) is a disease-specific instrument designed to measure aspects of health that are relevant to subjects with PD, and which may not be included in general health status questionnaires. Each item is scored on the following 5-point scale: 0 = never, 1 = occasionally, 2 = sometimes, 3 = often, 4 = always (or cannot do at all, if applicable).

Higher scores are consistently associated with more severe symptoms of the disease such as tremors and stiffness. The results are presented as 8 discrete domain scores and as a summary index. The PDQ-39 domain scores and summary index range from 0 to 100, where lower scores indicate a better perceived health status.

A qualified rater will administer the PDQ-39 at the visits specified in Section 2. The PDQ-39 will be administered prior to initiation of the CSCI of ABBV-951 on Day 1 (V3).

Movement Disorder Society-Unified Parkinson's Disease Rating Scale

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is an investigator-used rating tool to follow the longitudinal course of PD. Every effort should be made by the study sites to ensure that each subject is rated by the same rater throughout the subject's participation in the study. The MDS-UPDRS assessment will be performed by an approved, trained rater. To be qualified by the sponsor and the rater vendor, all raters must have participated in the rater training and have a current valid rater certificate.

The MDS-UPDRS consists of the following sections:

- Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

- Part II: Motor Aspects of Experiences of Daily Living (M-EDL)
- Part III: Motor Examination (including Hoehn and Yahr stage)
- Part IV: Motor Complications

Some sections require that multiple grades be assigned to each extremity. The MDS-UPDRS total score (Parts I-III) ranges from 0 to 236 with 236 representing the worst (total) disability, and 0 representing no disability.

For the duration of the study, the MDS-UPDRS will be administered in the subjects' best "On" state with the exception of Day 1 (V3). Before starting the infusion of the investigational drug, subjects will initially complete the MDS-UPDRS Part III in a practically defined "Off" state (i.e., without having taken any anti-PD medication since the evening of the day before the visit). The assessment should be repeated after initiation of the infusion during the subject's best "On" state, which should be 1 to 2 hours after the beginning of the ABBV-951 infusion. If possible, the MDS-UPDRS should be done at the same time of day at each visit throughout the trial by a qualified rater. At all indicated visits specified in Section 2, a complete MDS-UPDRS (Parts I through IV) will be done during "On" time.

Unified Parkinson's Disease Rating Scale

In countries where a validated translation of the MDS-UPDRS scale is not available, the Unified Parkinson's Disease Rating Scale (UPDRS) version will instead be used.

The UPDRS is an investigator-used rating tool to follow the longitudinal course of PD. Every effort should be made by the investigative sites to ensure that each subject is rated by the same rater throughout the subject's participation in the study. The UPDRS assessment will be performed by an approved, trained rater. To be qualified by the sponsor and the rater vendor, all raters must have participated in rater training and have a current valid rater certificate.

The UPDRS consists of the following sections:

- Part I Mentation, Behavior, and Mood
- Part II Activities of Daily Living
- Part III Motor Examination
- Part IV Complications of Therapy (including dyskinesias)
- Part V Modified Hoehn and Yahr Staging

For the duration of the study, the UPDRS will be administered in the subject's best "On" state with the exception of Day 1 (V3). Before starting the infusion of the investigational drug, subjects will initially complete the UPDRS Part III in a practically defined "Off" state (i.e., without having taken any anti-PD medication since the evening of the day before the visit). The assessment should be repeated after initiation of the infusion during the subject's best "On" state, which should be 1 to 2 hours after the beginning of the ABBV-951 infusion. If possible, the UPDRS should be done at the same time of day at each visit throughout the trial by a qualified rater. At all indicated visits specified in Section 2, a complete UPDRS (Parts I through V) will be done during "On" time.

Parkinson's Disease Sleep Scale-2

Although a number of scales exist to evaluate sleep disturbances, only 3 are endorsed and recommended by the Movement Disorders Society. One such scale specific for PD is the Parkinson's

Disease Sleep Scale (PDSS), which has been modified to the PDSS-2. The purpose of the PDSS-2 is to characterize the various aspects of nocturnal sleep problems in patients with PD. 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. The PDSS-2 consists of 15 questions that evaluate motor and non-motor symptoms at night and upon wakening, as well as disturbed sleep grouped into 3 domains: motor symptoms at night (5 items), PD symptoms at night (5 items), and disturbed sleep (5 items). Specifically, the questions assess overall sleep quality, insomnia, sleep fragmentation, restless leg syndrome (RLS) and periodic leg movements of sleep (PLMS), rapid eye movement behavior disorder (RBD), hallucinations, nocturia, nocturnal immobility, pain and cramps, morning akinesia, tremor, and sleep apnea. The PDSS-2 was developed from the PDSS based upon the need for a treatment measuring tool containing PD-specific sleep disorders; the instrument was extended to address specific sleep disturbances such as RLS, akinesia, pain, and sleep apnea. Daytime sleepiness was removed from the PDSS-2, as it is a more complex PD symptom.

To increase ease of use, the visual analogue scale of the PDSS was transformed into a frequency measure in the PDSS-2. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often] with the exception of Question 1 score ranging from 0 [very often] to 4 [never]). Scores are calculated for each domain as well as a total score. The recall period is for the past week.

A qualified rater will administer the PDSS-2 at the visits specified in Section 2. The PDSS-2 will be administered prior to initiation of the CSCI of ABBV-951 on Day 1 (V3).

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a brief, 30-point questionnaire, administered by a trained rater, that provides a quantitative measure of cognitive mental status in adults and is used widely 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 MMSE will be used in this study to screen for cognitive impairment. The MMSE score ranges from 0 to 30 with lower scores indicating greater impairment. The subject must have a score ≥ 24 at Screening Visit 1 (V1) to be eligible for study participation. Subjects with MMSE scores 19 to 23 inclusive may still be enrolled in the study if, in the investigator's opinion, the cognitive impairment does not preclude the subject from completing study-required procedures. Subjects with moderate or severe impairment (MMSE scores of 18 or below) may not be enrolled. A qualified rater will administer the MMSE at Screening Visit 1 (V1) as shown in Section 2.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale

The QUIP-RS is a brief, self-completed or rater-administered rating scale to assess the severity of symptoms of impulse control disorders (ICDs) and related behaviors reported to occur in PD. In this study, QUIP-RS will be rater administered. The QUIP-RS can also aid in supporting a diagnosis of ICDs and related disorders in PD. The QUIP-RS uses a 5-point Likert scale that requires individuals to rate the severity of each symptom based on its frequency. The potential advantages to using a rating scale include detection of subsyndromal behaviors, establishment of clear cutoff points with a good balance between sensitivity and specificity, and the ability to monitor changes in symptoms over time.

The QUIP-RS has 4 primary questions (pertaining to commonly reported thoughts, urges/desires, and behaviors associated with ICDs), each applied to the 4 ICDs (compulsive gambling, buying, eating, and

sexual behavior) and 3 related disorders (medication use, punding, and hobbyism). It uses a 5-point Likert scale (score 0 – 4 for each question) to gauge the frequency of behaviors, and instructs patients to answer questions based on behaviors that occurred in the preceding 4 weeks (or any 4-week period in a designated time frame). The QUIP-RS is administered with an instruction sheet that provides examples of the behaviors being assessed and a brief description of the Likert scale categories for frequency (i.e., never [0] = not at all, rarely [1] = infrequently or 1 day/week, etc.). Scores for each ICD and related disorder range from 0 to 16, with a higher score indicating greater severity (i.e., frequency) of symptoms. Due to overlap, hobbyism and punding were combined in the validation process to form a single diagnosis (hobbyism-punding), with a total score ranging from 0 to 32 for the combined disorder. The total QUIP-RS score for all ICDs and related disorders combined ranges from 0 to 112.

The behaviors can be described as:

(i) Gambling (casinos, internet gambling, lotteries, scratch tickets, betting, or slot or poker machines);
(ii) Sex (making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography);
(iii) Buying (too much of the same thing or things that you don't need or use);
(iv) Eating (eating larger amounts or different types of food than in the past, more rapidly than normal, until feeling uncomfortably full, or when not hungry);
(v) Hobbyism (specific tasks, hobbies or other organized activities, such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.);
(vi) Punding (repeating certain simple motor activities, such as cleaning, tidying, handling, examining, sorting, ordering, collecting, hoarding, or arranging objects, etc.);
(vii) Medication use (consistently taking too much of your Parkinson's medications, or increasing on your own, without medical advice, your overall intake of Parkinson's medications)

The frequency of behaviors are described as never (0) = not at all, rarely; (1) = infrequently or 1 day/week; sometimes (2) = at times or 2 to 3 days/week; often (3) = most of the time or 4 – 5 days/week; very often (4) = nearly always or 6-7 days/week.

A qualified rater will administer the QUIP-RS at the times described in Section 2.

Parkinson's KinetiGraph

Developed by Global Kinetics Corporation, the Parkinson's KinetiGraph™ system (PKG™ or Personal KinetiGraph™ as it is known in the US), is an innovative mobile health technology. The PKG™ provides continuous, objective, ambulatory assessment of the symptoms of PD including tremor, bradykinesia, and dyskinesia. The PKG™ also provides an assessment of daytime somnolence and an indication of propensity for impulsive behaviors. The PKG™ system consists of a wrist-worn movement recording device known as the PKG™-Watch, proprietary algorithms, and a data-driven report known as the PKG™. Data are collected continuously by the PKG™-Watch during activities of daily living in the home environment. The PKG™-Watch should be worn by the subject continuously except for recharging once a week (e.g., the night of the 7th day, every week). The data are uploaded for processing at the time of recharging.

As allowed by local regulations, subjects will receive the PKG-watch following Visit 1 (V1), after being received by the study site, and prior to the Monitoring Period. The Monitoring Period can occur any time before V3, as long as it lasts for 6 consecutive days. Subjects will be required to wear the PKG-watch (refer to the currently approved manufacturer's directions) for at least the 6-day Monitoring Period during the Screening Period to at least the Week 26 Visit (V11); thereafter, wearing of the

PKG-watch will be optional. "As allowed by local regulations" is applicable to all wearable device references throughout this protocol and its appendices. The AbbVie TA MD should be consulted if, in the opinion of the Investigator, there are circumstances that might interfere with the use of the PKG device (e.g., religious reasons, atopic dermatitis). A subject's inability to wear the PKG watch, due to logistics hindering the watch from being made available, will not preclude him/her from study participation. During the 6-day Monitoring Period, subjects should be active (engaged in usual activities of daily living and not sitting or resting on a couch or chair or lying in bed) for at least 30 minutes before taking their first oral dose.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, PROs eligible for completion at the study visits for Weeks 1, 2, 3, 4, 13, and 39 may be conducted remotely. In this situation, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by video conference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with the name of the individual who collected the information.

3.11 Clinical Laboratory Tests

Samples for clinical laboratory tests will be collected at the visits specified in Section 2. The Day 1 (V3) samples will be collected prior to initiation of the CSCI of ABBV-951. The last laboratory test results prior to initiation of the CSCI will serve as the Baseline for clinical assessment for a particular test.

A certified central laboratory will be used to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study. Follow-up safety laboratory tests may be performed by a certified laboratory other than the site's local laboratory.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory via the laboratory manual.

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine[a]	Ketones
Red blood cell (RBC) count	Creatine phosphokinase	pH
White blood cell (WBC) count	Total bilirubin	Protein
Neutrophils	Serum glutamic pyruvic transaminase	Glucose
Bands (if detected)		Blood
Lymphocytes	Serum glutamic-oxaloacetic transaminase	Bilirubin
Monocytes		Microscopic examination, if indicated
Basophils (if detected)	Lactate dehydrogenase (LDH)	
Eosinophils (if detected)	Gamma-glutamyl transpeptidase	
Absolute platelet count	Alkaline phosphatase	
Mean corpuscular hemoglobin	Sodium	
Mean corpuscular volume concentration (MCHC)	Potassium	
	Calcium	
Prothrombin time (PT)	Inorganic phosphorus	
Activated partial thromboplastin time	Uric acid	
	Total protein	
	Albumin	
	Glucose	
	Sodium bicarbonate/CO_2	
	Chloride	
	Triglycerides	
	Cholesterol	
	Magnesium	
	Special Laboratory Tests[b]	
	Vitamin B_6	
	Vitamin B_{12}	
	Folic acid	
	Methylmalonic acid (MMA)	
	Homocysteine	

GFR = glomerular filtration rate

a. GFR will be calculated one time at Screening Visit 1 (V1) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

b. Special laboratory tests to detect vitamin deficiencies, i.e., vitamin B_{12}, vitamin B_6, folic acid, homocysteine, and MMA levels will be performed at Screening Visit 1 (V1), on Day 1 (V3), and at Week 6 (V9), Week 26 (V11), and Week 52 (V13). An abnormal vitamin B_{12} level of questionable clinical significance (indeterminate or low normal results at Screening Visit 1 [V1]), requires MMA and homocysteine laboratory assessments to be reviewed for determination of vitamin B_{12} deficiency prior to entry into the study. If, at any time during the study, a subject displays symptoms of polyneuropathy, the investigator must perform this laboratory panel and any other assessment that the investigator feels is appropriate for further evaluation of polyneuropathy symptoms.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or

- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an AE.

All laboratory abnormalities that occur during the study must be evaluated by the investigator to determine if they indicate a new disease process, an exacerbation or worsening of an existing condition, or require further action and therefore may need to be reported as AEs. Accordingly, for any values outside of the reference range, the investigator will indicate on the report if the result is clinically significant or not clinically significant. If a laboratory abnormality meets criteria for a potentially clinically significant (PCS) laboratory value, the investigator must either report an associated AE or document in source the reason(s) the finding was not considered an AE. See Appendix A.

Any laboratory value that remains abnormal at premature discontinuation/end of study and was judged to be clinically significant will be followed according to accepted medical standards until resolution of the abnormality.

Serum and Urine Pregnancy Tests

A pregnant or breastfeeding female subject will not be eligible for participation or continuation in this study.

Pregnancy testing is not required for females of non-childbearing potential. Determination of post-menopausal status will be made during the Screening Period based on the subject's history.

A serum pregnancy test will be performed at V1 and a urine pregnancy test will be performed as shown in Section 2 for all women of childbearing potential. The urine sample for the Day 1 (V3) urine pregnancy test will be collected prior to initiation of the CSCI of ABBV-951.

The serum pregnancy test will be performed by the central laboratory. Urine pregnancy tests will be performed and analyzed at the site during the study visit if there is a scheduled visit. If there is not a scheduled visit, subjects may either have a pregnancy test at the site as an unscheduled visit or at home with a pregnancy test kit provided by the site. If a urine pregnancy test is performed at home, site personnel will contact the subject to capture the results of any study-related pregnancy tests and record these results in the source records only. If a urine pregnancy test is positive, the results should be confirmed with a serum hCG test that will be performed by the central laboratory.

If the serum pregnancy test at V1 is positive, the subject is considered a screen failure. If the result of the serum pregnancy test is borderline, it should be repeated to determine eligibility.

If the pregnancy test is:

- Positive after the serum pregnancy confirmation, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the study;
- Still borderline, the AbbVie TA MD should be consulted.

Clinical Chemistry

An 8-hour fast is recommended for blood samples to be drawn for clinical chemistry. If a subject is not able to fast when necessary due to unforeseen circumstances, the nonfasting status will be recorded in study source documentation.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. The investigator should review local laboratory results as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.

3.12 Subject Withdrawal from Study

All attempts must be made to determine the date of the end of the infusion of study drug and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate electronic case report form (eCRF) page; however, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

3.13 Biomarker Sampling

Optional samples for biomarker testing will be collected at the visits specified in Section 2. All samples should be labeled and shipped as outlined in the study-specific laboratory manual.

3.14 12-Lead Electrocardiogram

Single electrocardiograms (ECGs) will be recorded at the visits specified in Section 2 after the subject has been supine for at least 5 minutes. Subjects will be instructed to remain stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. When an ECG is recorded at a time near that of a blood collection, the ECG should be obtained prior to the

blood collection. ECGs on Day 1 (V3) will be recorded after initiation of the CSCI of ABBV-951 prior to the end of the visit.

Clinical study personnel will transmit ECG data to an ECG central laboratory for processing and reading by a qualified cardiologist (central reader) who will independently review each ECG. The central reader will evaluate a single ECG lead (Lead II, with V5 or V2 [in that order] evaluated if Lead II cannot be evaluated). Heart rate, RR interval, PR interval, QRS duration, and QT interval will be measured for each ECG with 3 to 5 beats. QT interval corrected for heart rate (QTc) will be determined using Fridericia's correction method (QTcF).

The central reader will also provide the interpretation of the ECG (i.e., "normal" or "abnormal"). The central ECG laboratory will send the ECG report to the site within 3 business days. The investigator (or physician designee) will review the central reader's report/assessment and document his/her review by signing and dating the central ECG laboratory report. Only the central ECG laboratory's data will be collected into the database. The investigator should review and reconcile if necessary his/her interpretation of the ECG (normal/abnormal) with the central ECG laboratory in case of relevant divergent assessments and reconcile as he/she determines is appropriate.

The original ECG tracing and the central reader's interpretation, each with the investigator's signature and date, will be retained in the subject's records at the study site as source documents.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that an ECG may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

3.15 Vital Signs

Vital signs will be collected for both clino and orthostatism (supine and standing). For clino vital signs, blood pressure and pulse rate will be measured after the subject has been supine for at least 5 minutes. For orthostatic vital signs, blood pressure and pulse rate will be measured after the subject has been supine for at least 5 minutes and then, after the subject has been standing for 2 minutes. When vital sign measurements are scheduled at the same time as a blood collection, vital sign measurements should be obtained prior to blood collection.

Vital signs will be measured at the visits specified in Section 2. Orthostatic vital signs will be measured on Day 1 (V3), and at Week 1 (V5), Week 6 (V9), Week 26 (V11), and Week 52 (V13) (or premature discontinuation). Vital signs on Day 1 (V3) will be measured after initiation of the CSCI of ABBV-951 prior to the end of the visit.

See Appendix B for criteria for PCS vital sign values.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted remotely. In these situations, vital signs may be obtained by the subject as needed and recorded in the subject's source documentation.

These data should not be recorded in EDC, as data are not obtained on calibrated devices and may not be obtained by medically trained individuals.

3.16 Height and Weight

Height and body weight will be measured at Screening Visit 1 (V1) as shown in Section 2. Height will be measured at Screening Visit 1 (V1) only; weight will measured at the visits specified in Section 2. The subject should not wear shoes during either measurement.

See Appendix B for criteria for PCS weight values.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted remotely. In these situations, height and weight measurements may be performed by the subject as needed and recorded in the subject's source documentation. These data should not be recorded in EDC, as data are not obtained on calibrated devices and may not be obtained by medically trained individuals.

3.17 Physical Examination

A complete physical examination will be performed at Screening Visit 1 (V1), on Day 1 (V3), and at Week 6 (V9), Week 26 (V11), and Week 52 (V13) as shown in Section 2. The physical examination performed at Screening Visit 1 (V1) will serve as the baseline physical examination for clinical assessment. A symptom-directed physical examination will be performed at each following visit when necessary. Any significant physical examination findings after dosing will be recorded as AEs.

3.18 Neurological Examination

A neurological examination will be performed at the visits shown in Section 2. Neurological findings beyond those related to PD should be reported in the eCRF. The neurological examination performed at Screening Visit 1 (V1) will serve as the Baseline for clinical assessment. Any significant neurological findings after dosing will be recorded as AEs.

The neurological examination will consist of the following:

- Mental status – assessment of orientation, speech, and memory.
- Cranial nerves – assessment of cranial nerves II – XII, including a funduscopic examination.
- Motor system – assessment of tone and strength.
- Sensory system – brief survey for light touch and temperature.
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign).
- Coordination – assessment of upper and lower extremities.
- Gait and station.

3.19 Drug Delivery System Training

AbbVie personnel, or its delegate, will train the site how to calculate each subject's LED, to program the pump to administer the continuous dose and to titrate the dose for each subject as needed. In addition, the site will be trained to prepare the drug delivery system by (i) loading the study drug into the syringe, (ii) placing it into the pump, (iii) attaching the infusion set to the subject and syringe, (iv) priming the syringe and infusion set, and (v) operating the pump. Clinical study personnel will receive the ABBV-951 System User Manual and the ABBV-951 System Programming Guide.

Subjects will receive training on the drug delivery system (e.g., pump, infusion set, syringe, vial, and vial adapter) at the visits specified in Section 2. Training on Day 1 (V3) will occur prior to initiation of the CSCI of ABBV-951. In addition to training, subjects will receive training materials for reference.

Subjects may be trained at Screening Visit 2 (V2) by site staff or nurses contracted by the sponsor on use of the drug delivery system. These nurses must be trained on how to use the drug delivery system prior to training study subjects. In addition, subjects may receive in-home visits from nurses to provide additional training and support with the drug delivery system. During these in-home visits, the home health care nurse may ask questions about any problems or concerns the subject is having using the drug delivery system. The home health care nurse will record the subject's answers and provide these to the study site for review.

3.20 Drug Delivery System Dispensing and Return

Study drug is intended to be dispensed to subjects every 2 weeks during the Treatment Period with or without a clinic visit being completed. The drug delivery system, including tubing and other accessories will be dispensed as needed.

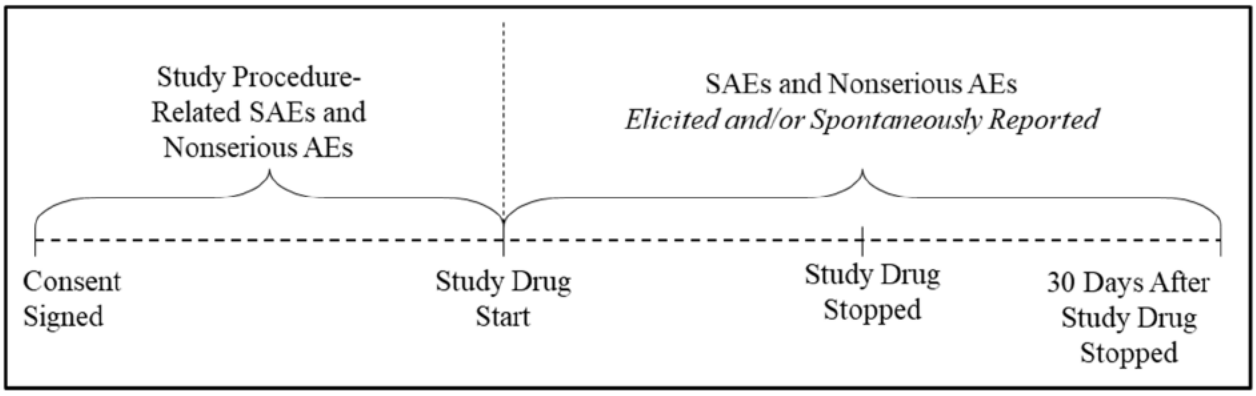
Additionally, a subject (or authorized representatives, if allowed per local regulations) may return to the clinic site for additional study drug or drug delivery system components or accessories.

For eligible subjects at participating sites, and as allowed by local regulations, the study drug, its delivery system and accessories may be directly delivered to the subject's preferred address by a third party vendor contracted by the sponsor.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious AEs that could be related to study procedures will be collected from the time the subject signs the study-specific informed consent until the start of study drug infusion. From the start of study drug infusion until 30 days after discontinuation of study treatment, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours after the site becomes aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 847-938-0660

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Safety Team, [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Office: +1 847-938-4191
Email: SafetyManagement_Neuroscience@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary AbbVie TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

HOTLINE: +1 973-784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with Directive 2001/20/EC.

Supplemental study case report forms should be completed in the event of COVID-19-related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

4.3 Product Complaint Reporting

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours day of the study site's knowledge of the event. Product complaints occurring during the study will be followed to a satisfactory conclusion.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required (refer to Protocol Section 6.1, Complaints and Adverse Events for details).

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 Sample Retention Requirements

AbbVie (or people or companies working with AbbVie) will store the optional biomarker samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABBV-951 (or drugs of this class) or PD and related conditions continues, but for no longer than 20 years after study completion or according to local requirements.

5.2 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the IMP in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a Development Safety Update Report reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the "suspected" Serious Adverse Reaction will be used to assess expectedness.

5.3 Treatment After End of Study

At the end of the study, subjects may continue on study treatment as part of an open-label extension study. At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject.

6 REFERENCES

1. Antonini A, Schmidt P, Odin P, et al. Development of a clinician-reported screening tool to identify patients with Parkinson's disease inadequately controlled on oral medications [abstract]. Mov Disord. 2017;32 (suppl 2). Available from: http://www.mdsabstracts.org/abstract/development-of-a-clinician-reported-screening-tool-to-identify-patients-with-parkinsons-disease-inadequately-controlled-on-oral-medications/. Accessed on: June 19, 2017.
2. Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. US Dept of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). December 1999.

APPENDIX A. NEUROLOGY LABORATORY GRADING

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology						
Activated partial thromboplastin time (aPTT) prolonged	1	**> ULN**	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN; hemorrhage	--
Anemia (hemoglobin decreased)	2	**< 100 g/L (i.e., < 10 g/dL, < 6.2 mmol/L)**	< LLN – 100 g/L (i.e., < LLN – 10 g/dL, < LLN – 6.2 mmol/L)	< 100 – 80 g/L (i.e., < 10 – 8 g/dL, < 6.2 – 4.9 mmol/L)	< 80 g/L (i.e., < 8 g/dL, < 4.9 mmol/L); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Hemoglobin increased	3	**> 40 g/L above ULN**	Increase in > 0 – 20 g/L above ULN **or** above baseline if baseline is above ULN	Increase in > 20 – 40 g/L above ULN **or** above baseline if baseline is above ULN	Increase in > 40 g/L above ULN **or** above baseline if baseline is above ULN	--
INR increased	1	**> ULN**	> 1 – 1.5 × ULN **or** > 1 – 1.5 times above baseline if on anticoagulation	> 1.5 – 2.5 × ULN **or** > 1.5 – 2.5 times above baseline if on anticoagulation	> 2.5 × ULN **or** > 2.5 times above baseline if on anticoagulation	--
Leukocytosis (WBC increased)	3	**> 100 × 10^9/L (i.e., > 100,000/mm^3)**	--	--	> 100× 10^9/L (i.e., > 100,000/mm^3)	Clinical manifestations of leukostasis; urgent intervention indicated
Lymphocyte count decreased	3	**< 0.5 × 10^9/L (i.e., < 500/mm^3)**	< LLN – 0.8 × 10^9/L (i.e., < LLN – 800/mm^3)	< 0.8 – 0.5 × 10^9/L (i.e., < 800 – 500/mm^3)	< 0.5 – 0.2 × 10^9/L (i.e., < 500 – 200/mm^3)	< 0.2 × 10^9/L (i.e., < 200/mm^3)

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Lymphocyte count increased	3	**> 20× 10^9/L (i.e., > 20,000/mm^3)**	--	> 4 – 20× 10^9/L (i.e., > 4000 – 20,000/mm^3)	> 20× 10^9/L (i.e., > 20,000/mm^3)	--
Neutrophil count decreased	3	**< 1 × 10^9/L (i.e., < 1000/mm^3)**	< LLN – 1.5 × 10^9/L (i.e., < LLN – 1500/mm^3)	< 1.5 – 1 × 10^9/L (i.e., < 1500 – 1000/mm^3)	< 1– 0.5 × 10^9/L (i.e., < 1000 – 500/mm^3)	< 0.5 × 10^9/L (i.e., < 500/mm^3)
Platelet count decreased	2	**< 75 × 10^9/L (i.e., < 75,000/mm^3)**	< LLN – 75× 10^9/L (i.e., < LLN – 75,000/mm^3)	< 75 – 50 × 10^9/L (i.e., < 75,000 – 50,000/mm^3)	< 50 – 25 × 10^9/L (i.e., < 50,000 – 25,000/mm^3)	< 25 × 10^9/L (i.e., < 25,000/mm^3)
White blood cell decreased	3	**< 2× 10^9/L (i.e., < 2000/mm^3)**	< LLN – 3× 10^9/L (i.e., < LLN – 3000/mm^3)	< 3 – 2 × 10^9/L (i.e., < 3000 – 2000/mm^3)	< 2 – 1 × 10^9/L (i.e., < 2000 – 1000/mm^3)	< 1 × 10^9/L (i.e., < 1000/mm^3)
Chemistry						
Blood bilirubin increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Cholesterol high	4	**> 12.92 mmol/L (i.e., > 500 mg/dL)**	> ULN – 7.75 mmol/L (i.e., > ULN – 300 mg/dL)	> 7.75 – 10.34 mmol/L (i.e., > 300 – 400 mg/dL)	> 10.34 – 12.92 mmol/L (i.e., > 400 – 500 mg/dL)	> 12.92 mmol/L (i.e., > 500 mg/dL)
Creatinine increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN or > 1 – 1.5 × baseline	> 1.5 – 3 × ULN or > 1.5 – 3 × baseline	> 3 – 6 × ULN or > 3 × baseline	> 6 × ULN
Gamma-Glutamyl Transpeptidase (GGT) increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20× ULN

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
		Corrected Serum Calcium of:				
Hypercalcemia	3	**> 3.1 mmol/L (i.e., > 12.5 mg/dL)**	> ULN – 2.9 mmol/L (i.e., > ULN – 11.5 mg/dL)	> 2.9 – 3.1 mmol/L (i.e., > 11.5 – 12.5 mg/dL)	> 3.1 – 3.4 mmol/L (i.e., > 12.5 – 13.5 mg/dL)	> 3.4 mmol/L (i.e., > 13.5 mg/dL)
		Ionized Calcium				
		> 1.6 mmol/L	> ULN – 1.5 mmol/L	> 1.5 – 1.6 mmol/L; symptomatic	> 1.6 – 1.8 mmol/L; hospitalization indicated	> 1.8 mmol/L; life-threatening consequences
		Fasting Glucose Value				
Hyperglycemia	3	**> 13.9 mmol/L (i.e., > 250 mg/dL)**	> ULN – 8.9 mmol/L (i.e., > ULN – 160 mg/dL)	> 8.9 – 13.9 mmol/L (i.e., > 160 – 250 mg/dL)	> 13.9 – 27.8 mmol/L; (i.e., > 250 – 500 mg/dL) hospitalization indicated	> 27.8 mmol/L (i.e., > 500 mg/dL); life-threatening consequences
Hyperkalemia	3	**> 6 mmol/L**	> ULN – 5.5 mmol/L	> 5.5 – 6 mmol/L	> 6 – 7 mmol/L; hospitalization indicated	> 7 mmol/L; life-threatening consequences
Hypermagnesemia	3	**> 1.23 mmol/L (i.e., > 3 mg/dL)**	> ULN – 1.23 mmol/L (i.e., > ULN – 3 mg/dL)	--	> 1.23 – 3.30 mmol/L (i.e., > 3 – 8 mg/dL)	> 3.30 mmol/L consequences (i.e., > 8 mg/dL); life-threatening
Hypernatremia	3	**> 155 mmol/L**	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L; hospitalization indicated	> 160 mmol/L; life-threatening consequences
Hypertriglyceridemia	3	**> 5.7 mmol/L (i.e., > 500 mg/dL)**	1.71 – 3.42 mmol/L (i.e., 150 – 300 mg/dL)	> 3.42 – 5.7 mmol/L (i.e., > 300 – 500 mg/dL)	> 5.7 – 11.4 mmol/L (i.e., > 500 – 1000 mg/dL)	> 11.4 mmol/L (i.e., > 1000 mg/dL); life-threatening consequences

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hyperuricemia (uric acid increased)	4	**> 0.59 mmol/L (i.e., > 10 mg/dL)**	> ULN – 0.59 mmol/L (10 mg/dL) without physiologic consequences	--	> ULN – 0.59 mmol/L (10 mg/dL) with physiologic consequences	> 0.59 mmol/L (i.e., > 10 mg/dL); life-threatening
Hypoalbuminemia	3	**< 20 g/L**	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	Life-threatening consequences; urgent intervention indicated
		Corrected Serum Calcium				
Hypocalcemia	3	**< 1.75 mmol/L (i.e., < 7 mg/dL)**	< LLN – 2 mmol/L (i.e., < LLN – 8 mg/dL)	< 2 – 1.75 mmol/L (i.e., < 8 – 7 mg/dL)	< 1.75 – 1.5 mmol/L (i.e., < 7 – 6 mg/dL)	< 1.5 mmol/L (i.e., < 6 mg/dL)
		Ionized Calcium				
		< 0.9 mmol/L	< LLN – 1 mmol/L	< 1 – 0.9 mmol/L; symptomatic	< 0.9 – 0.8 mmol/L; hospitalization indicated	< 0.8 mmol/L; life-threatening consequences
Hypoglycemia	3	**< 2.2 mmol/L (i.e., < 40 mg/dL)**	< LLN – 3 mmol/L (i.e., < LLN – 55 mg/dL)	< 3 – 2.2 mmol/L (i.e., < 55 – 40 mg/dL)	< 2.2 – 1.7 mmol/L (i.e., < 40 – 30 mg/dL)	< 1.7 mmol/L (i.e., < 30 mg/dL); life-threatening consequences; seizures
Hypokalemia	3	**< 3 mmol/L**	< LLN – 3 mmol/L	< LLN – 3 mmol/L; symptomatic; intervention indicated	< 3 – 2.5 mmol/L; hospitalization indicated	< 2.5 mmol/L; life-threatening consequences
Hypomagnesemia	3	**< 0.4 mmol/L (i.e., < 0.9 mg/dL)**	< LLN – 0.5 mmol/L (i.e., < LLN – 1.2 mg/dL)	< 0.5 – 0.4 mmol/L (i.e., < 1.2 – 0.9 mg/dL)	< 0.4 – 0.3 mmol/L (i.e., < 0.9 – 0.7 mg/dL)	< 0.3 mmol/L (i.e., < 0.7 mg/dL); life-threatening consequences

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	3	**< 130 mmol/L**	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L; life-threatening consequences
Hypophosphatemia	3	**< 0.6 mmol/L (i.e., < 2 mg/dL)**	< LLN – 0.8 mmol/L (i.e., < LLN – 2.5 mg/dL)	< 0.8 – 0.6 mmol/L (i.e., < 2.5 – 2 mg/dL)	< 0.6 – 0.3 mmol/L (i.e., < 2 – 1 mg/dL)	< 0.3 mmol/L (i.e., < 1 mg/dL); life-threatening consequences
Enzymes						
Alanine aminotransferase (ALT) increased	2	**> 3 × ULN**	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline phosphatase increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Aspartate aminotransferase (AST) increased	2	**> 3 × ULN**	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Creatine Phosphokinase (CPK) increased	3	**> 5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 10 × ULN	> 10 × ULN

Adapted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

INR = international normalized ratio; LLN = lower limit of normal; PCS = potentially clinically significant; ULN = upper limit of normal; WBC = white blood cells

APPENDIX B. CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGN VALUES AND WEIGHT VALUES

Variable Measured	Potentially Clinically Significant (PCS) Value
Vital Sign	
Diastolic blood pressure decreased	≤ 50 mmHg and ≤ 40 mmHg below baseline value
Diastolic blood pressure increased	≥ 95 mmHg and ≥ 40 mmHg above baseline value
Orthostatic diastolic blood pressure	≥ 20 mmHg decrease from supine to standing
Pulse rate decreased	≤ 45 bpm and ≤ 35 bpm below baseline value
Pulse rate increased	≥ 120 bpm and ≥ 35 bpm above baseline value
Systolic blood pressure decreased	≤ 80 mmHg and ≤ 45 mmHg below baseline value
Systolic blood pressure increased	≥ 160 mmHg and ≥ 45 mmHg above baseline value
Orthostatic systolic blood pressure	≥ 30 mmHg decrease from supine to standing
Temperature increased	≥ 38.3°C and ≥ 1.1°C above baseline value
Weight decreased	≥ 7% decrease from baseline value
Weight increased	≥ 7% increase from baseline value

bpm = beats per minute

Document Approval

Study M15741 - A 52-Week, Open-Label, Single-Arm Study to Evaluate the Safety and Tolerability of 24-Hour Daily Exposure of Continuous Subcutaneous Infusion of ABBV-951 in Subjects with Parkinson's Disease - Protocol Version 7-0 - EudraCT 2018-002144-85 - 11Feb2021

Version: 1.0 **Date:** 11-Feb-2021 08:31:02 PM **Company ID:** 02112021-00F9F684A19B6F-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	11-Feb-2021 01:49:40 PM	Approver
	11-Feb-2021 02:07:13 PM	Approver
	11-Feb-2021 02:26:08 PM	Approver
	11-Feb-2021 02:52:46 PM	Author
	11-Feb-2021 03:04:56 PM	Approver
	11-Feb-2021 04:53:05 PM	Approver
	11-Feb-2021 08:31:02 PM	Approver