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Protocol for Study M15-736

Advanced Parkinson's Disease: Double-Blind, Double-Dummy, Active-Controlled, Efficacy and Safety Study of ABBV-951 Versus Oral Carbidopa/Levodopa

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FULL TITLE: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients

Incorporating Versions 1.0, 2.0, 3.0, 4.0, and 5.0.

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1 SYNOPSIS

Title: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients	
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). This study is conducted to assess the efficacy, safety, and tolerability of ABBV-951 versus oral CD/LD in subjects with advanced Parkinson's disease (aPD) whose motor fluctuations are inadequately controlled by their current treatment.

Objectives and Endpoints:	Primary Objective:
	• To demonstrate the superiority of CSCI of ABBV-951 over oral CD/LD immediate release (IR) tablets for the treatment of motor fluctuations in subjects with aPD after 12 weeks of therapy.
	Secondary Objective:
	• To assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for 12 weeks.
	Primary Endpoint:
	• Change from Baseline to Week 12 of the Double-Blind Treatment Period in "On" time without troublesome dyskinesia (hours) ("On" time without dyskinesia plus "On" time with non-troublesome dyskinesia), based on the PD Diary (normalized to a 16-hour waking day averaged over 3 consecutive days). The baseline value is defined as the average of normalized "On" time without troublesome dyskinesia collected over the 3 PD Diary days before randomization (V6).
	Key Secondary Endpoints:
	• Change from Baseline to Week 12 of the Double-Blind Treatment Period in:
	  • Hours of average daily normalized "Off" time as assessed by the PD Diary.
	  • Motor Aspects of Experiences of Daily Living (M-EDL) as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score.
	• Presence of morning akinesia at Week 12 (defined as reporting "Off" status as the first morning symptom upon awakening) as assessed by the PD Diary.
	Other Secondary Endpoints:
	• Change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia **as assessed by the**

	PD Diary. • Change from Baseline to Final Visit in sleep symptoms as assessed by the Parkinson's Disease Sleep Scale-2 (PDSS-2) total score. • Change from Baseline to Final Visit in PD-related quality of life as assessed by the Parkinson's Disease Questionnaire-39 item (PDQ-39) summary index. • Change from Baseline to Final Visit in health-related quality of life as assessed by the EQ-5D-5L summary index. • Change from Baseline to Week 12 in PD symptoms as assessed by the Parkinson's KinetiGraph®/Personal KinetiGraph® (PKG) wearable device (based on local country regulations). Safety endpoints are local tolerability (as measured by the Infusion Site Evaluation scale), adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), clinical laboratory values, vital signs, electrocardiograms (ECGs), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Questionnaire for Impulsive-Compulsive Disorders in PD – Rating Scale (QUIP-RS).
Investigators:	Multicenter
Study Sites:	Approximately 80 sites in the United States (US) and Australia
Study Population and Number of Subjects to be Enrolled:	Approximately 130 subjects with aPD whose motor fluctuations are inadequately controlled by their current treatment will be randomized
Investigational Plan:	Phase 3, randomized, double-blind, double-dummy, parallel group, active-controlled, multicenter study in an outpatient setting
Key Eligibility Criteria:	• 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 taking a minimum of 400 mg/day of LD equivalents and be judged by the investigator to have motor symptoms inadequately controlled by current therapy, have a recognizable/identifiable "Off" and "On" states (motor fluctuations), and have an average "Off" time of at least 2.5 hours/day over 3 consecutive PD Diary days with a minimum of 2 hours each day. • Subject (or caregiver, if applicable) demonstrates the understanding and correct use of the delivery system, including the insertion of the cannula into the subject's abdomen, as assessed by the investigator or designee during the Screening Period.

Study Drug and Duration of Treatment:	12 weeks treatment of • 24-hour/day CSCI of ABBV-951 plus oral placebo capsules for CD/LD IR OR • 24-hour/day CSCI of placebo solution for ABBV-951 plus encapsulated CD/LD IR tablets
Date of Protocol Synopsis:	10 September 2021

2 INTRODUCTION

2.1 Background and Rationale

Why This Study is Being Conducted

ABBV-951 (carbidopa phosphate/levodopa phosphate [CDP/LDP]) is soluble formulation of carbidopa/levodopa (CD/LD) prodrugs that is deliverable by continuous subcutaneous infusion (CSCI).

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

Systemic and local tolerability have been measured in animal models, and in the clinical setting with generally favorable outcomes. Local irritation was assessed in dogs at a CDP/LDP 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 or 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. 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. Skin adverse events (AEs) have been reported in other Phase 1 studies in subjects with PD where ABBV-951 was administered at therapeutic doses for 24 or 72 hours (Study M15-738) or for up to 28 days (Study M15-739). Most events have been mild in severity and manageable. No clinically concerning differences in skin tolerability were detected after 10 consecutive days of 48/960 mg CDP/LDP and an equivalent volume of saline infused over 24 hours/day in opposite sides of the abdomen in healthy volunteers (Study M18-763).

The dose ranges of ABBV-951 to be used in this study are similar to those administered in the Phase 1 studies in subjects with PD (Studies M15-738 and M15-739) and in the ongoing long-term safety study in aPD (Study M15-741).

This randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter, Phase 3 study will be conducted in an outpatient setting to evaluate efficacy, safety, and tolerability of a 24-hour/day CSCI of ABBV-951 versus oral CD/LD for 12 weeks in subjects with aPD.

2.2 Benefits and Risks to Subjects

The combination of oral LD and DOPA decarboxylase inhibitors, such as CD or benserazide, has been used for many years in patients with PD to control motor symptoms, and the systemic safety profile of CD/LD is well established. Achieving stable plasma LD 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 average daily "Off" time accompanied by increased "On" time without troublesome dyskinesia. Phase 1 studies showed that plasma LD concentrations from CSCI of ABBV-951 can be maintained stable and within the patient's therapeutic window.

Potential risks of receiving an ABBV-951 dose lower than the therapeutic dose required to control PD symptoms 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 the therapeutic dose include experiencing dyskinesias (abnormal or uncontrolled movements) and hallucinations. Other anticipated risks are well characterized LD-related side effects, including nausea, vomiting, and dizziness; however, not all of the potential side effects of ABBV-951 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 issues related to infusion site tolerability. This 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 and clinical studies (both in subjects with PD [Studies M15-738 and M15-739] and in healthy volunteers [Study M18-763]) show that infusion is generally well tolerated; however, the infusion rates (i.e., flow rates) in the current study are anticipated to be higher than those used in the study with healthy volunteers and to be delivered for a longer period of time compared with the studies in subjects with PD; therefore, assessment of local tolerability at the infusion site is a focus of this study.

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

ABBV-951 metabolizes into LD and CD, sharing the same characteristics of these compounds, which are commonly used as symptomatic treatment of PD globally. 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).

3 OBJECTIVES AND ENDPOINTS

Primary

- To demonstrate the superiority of CSCI of ABBV-951 over oral CD/LD immediate release (IR) tablets for the treatment of motor fluctuations in subjects with aPD after 12 weeks of therapy.

Clinical Hypothesis: The 24-hour/day CSCI of ABBV-951 will increase "On" time without troublesome dyskinesia, reduce "Off" time, and improve the Motor Aspects of Experiences of Daily Living (M-EDL) compared to CD/LD IR tablets in patients with aPD whose motor fluctuations are inadequately controlled by their current PD medications.

Secondary

- To assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for 12 weeks.

3.1 Primary Endpoint

The primary endpoint is the change from Baseline to Week 12 of the Double-Blind Treatment in "On" time without troublesome dyskinesia (hours) ("On" time without dyskinesia plus "On" time with non-troublesome dyskinesia), based on the PD Diary (normalized to a 16-hour waking day and averaged over 3 consecutive days). The baseline value is defined as the average of normalized "On" time without troublesome dyskinesia collected over the 3 PD Diary days before randomization (V6).

3.2 Secondary Endpoints

Key Secondary Endpoints

- Change from Baseline to Week 12 of the Double-Blind Treatment in:
  - Hours of average daily normalized "Off" time as assessed by the PD Diary.
  - M-EDL as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score.
- Presence of morning akinesia at Week 12 (defined as reporting "Off" status as the first morning symptom upon awakening) as assessed by the PD Diary.

Other Secondary Endpoints

- Change from Baseline to Week 12 in hours of average daily normalized “On” time without dyskinesia as assessed by the PD Diary.
- Change from Baseline to Final Visit in sleep symptoms as assessed by the Parkinson's Disease Sleep Scale-2 (PDSS-2) total score.
- Change from Baseline to Final Visit in PD-related quality of life as assessed by the Parkinson's Disease Questionnaire-39 item (PDQ-39) summary index.
- Change from Baseline to Final Visit in health-related quality of life as assessed by the EQ-5D-5L summary index.
- Change from Baseline to Week 12 in PD symptoms as assessed by the Parkinson's KinetiGraph®/Personal KinetiGraph® (PKG) wearable device (based on local country regulations).

3.3 Safety Endpoints

Safety endpoints are local tolerability (as measured by the Infusion Site Evaluation scale), AEs, serious AEs (SAEs), AEs of special interest (AESIs), clinical laboratory values, vital signs, electrocardiograms (ECGs), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

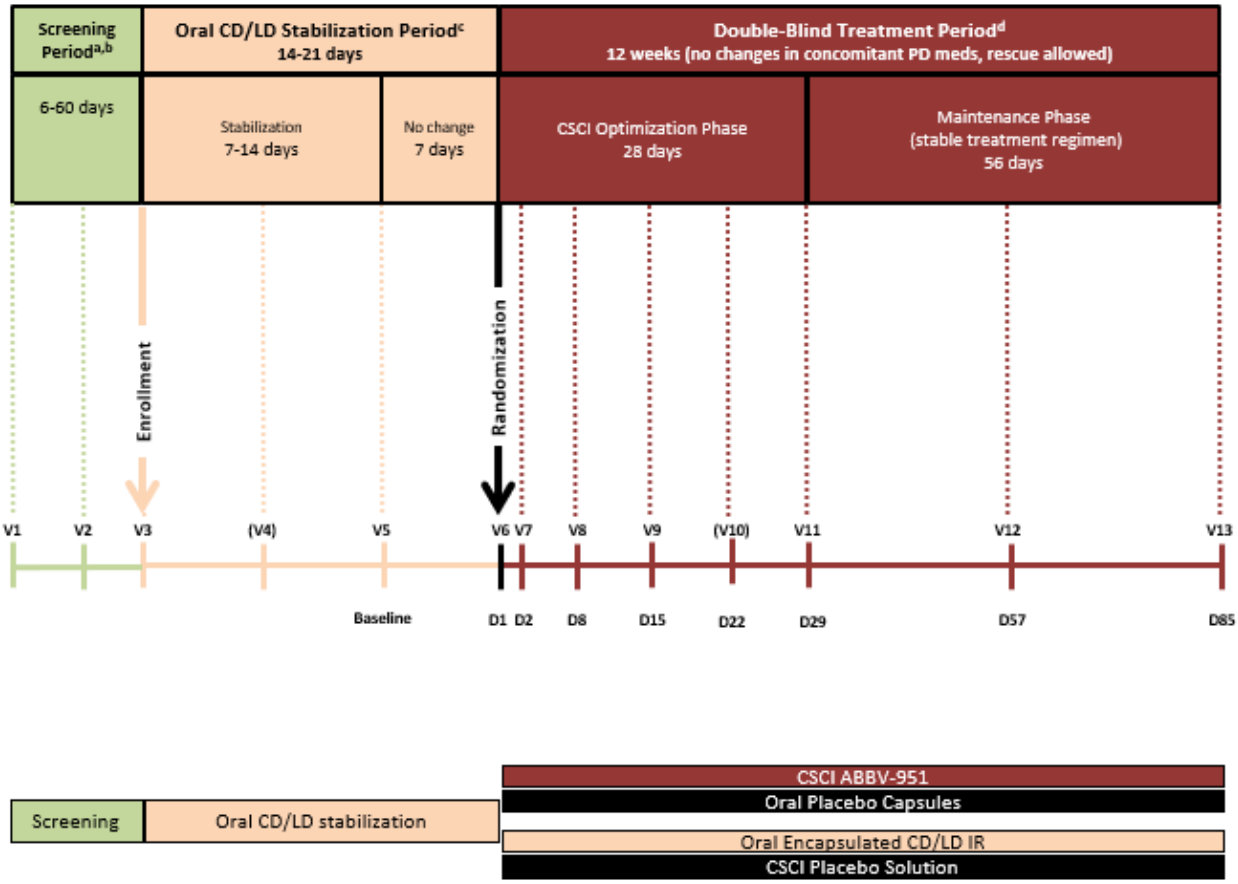
This is a Phase 3, randomized, double-blind, double-dummy, 12-week, parallel group, active-controlled, multicenter study assessing the efficacy, safety, and tolerability of 24-hour/day CSCI of ABBV-951 in the treatment of subjects with aPD whose motor fluctuations are inadequately controlled by their current medications. Approximately 130 adult subjects will be randomized in a 1:1 ratio to receive 24-hour/day CSCI of ABBV-951 plus oral placebo capsules or 24-hour/day CSCI of placebo solution plus oral encapsulated CD/LD IR tablets for 12 weeks. See Section 5.1 for eligibility criteria. Approximately 80 sites will participate.

Adverse events, clinical laboratory test results, ECGs, vital signs, and C-SSRS will be monitored throughout the study (see Section 3.6, Section 3.15, Section 3.14, Section 3.11, and Section 3.9, respectively, of the Operations Manual [Appendix F]).

The study consists of a Screening Period, an Oral CD/LD Stabilization Period, and a Double-Blind Treatment Period (randomization, CSCI Optimization Phase, Maintenance Phase). On the day of randomization, subjects will be required to arrive at the clinic in a practically defined "Off" state, i.e., after a 12-hour withdrawal of all PD medications. A schematic of the study is shown in Figure 1 (all timing is in calendar days). Details regarding study procedures are located in Section 3 of the Operations Manual (Appendix F).

The study includes 13 site visits. In rare situations where a visit cannot be completed onsite due to an extenuating event (e.g., genuine emergency, natural disaster, COVID-19-related disruptions), some assessments may be performed remotely or via a home health service. Refer to the Operations Manual (Appendix F) for further guidance.

Figure 1. Study Design Schematic



CD/LD = carbidopa/levodopa; CSCI = continuous subcutaneous infusion; D = Day; IR = immediate release; PD = Parkinson's disease; V = Visit

a. V3 should occur at least 6 days after V1 to allow test results from V1 results to be fully available for review and to provide adequate training and confirm the patient's familiarity with the infusion delivery system.

b. Screening Period activities will last at least 6 days; PD Diaries will be collected for at least 3 consecutive days during the Screening Period prior to V2; collection of PD Diaries may be repeated only once for 3 additional consecutive days leading up to V3 prior to the start of the Oral CD/LD Stabilization Period.

c. The activities of the Oral CD/LD Stabilization Period are expected to take 14 to 21 days to accommodate scheduling, additional unscheduled visits, and, when allowed, repeated assessments. PD Diaries will be collected for at least 3 consecutive days before Day –1).

d. If a subject prematurely discontinues study participation or completes the study and does not enter the open-label extension Study M20-098, a follow-up visit or follow-up phone call will be completed 30 days after the last day of study drug, if the subject is willing, to ensure all treatment-emergent AEs/SAEs have resolved.

Note: ***As allowed by local regulations, subjects will be required to wear the PKG watch (wearable device) (refer to the currently approved manufacturer's directions) from the beginning of V1 to Day 85 Visit (V13). "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).***

Screening Period (Duration: 6 to 60 Days)

The Screening Period includes 2 visits: Visit 1 (V1) and Visit 2 (V2). V3 should occur at least 6 days after V1 to allow test results from V1 to be fully available for review and to provide adequate training and confirm the patient's familiarity with the infusion delivery system. Screening Period activities are expected to take 6 to 60 days to accommodate scheduling and, when allowed, repeat assessments. The visits during this period are as follows:

- V1: Eligibility will be confirmed, including review of vitamin B_{12} requirements. Subjects with a low vitamin B_{12} or low-normal vitamin B_{12} and high MMA plasma level may undergo supplemental vitamin therapy. Retest for vitamin B_{12} is allowed during the Screening Period without repeating other screening procedures. Starting at V1, subjects (and caregivers, if applicable) will be trained on the correct use of the Phillips-Medisize Parkinson's Disease Subcutaneous (PM-PDSC) Pump Delivery System. V1 may be split into different visits.
- V2: Leading up to V2, subjects (and caregivers, if applicable), will continue to be trained on the correct use of the PM-PDSC Pump Delivery System at the study site or the subject's home. At V2, the subject (or caregiver) must demonstrate the understanding and correct use of the delivery system, including the insertion of the cannula into the subject's abdomen, which will be assessed by the investigator or designee using the PM-PDSC Knowledge and Skills Checklist. At the investigator or designee's discretion, the demonstration of understanding and correct use of the delivery system may be repeated at an unscheduled visit prior to the start of the Oral CD/LD Stabilization Period (V3). The Screening Period must not be extended beyond 60 days to accommodate this. Subjects who fail this requirement must be screen failed.

To increase familiarity with the PM-PDSC Pump Delivery System, subjects will have the opportunity to wear a mock infusion delivery system, where available, during the daily activities of the Screening Period. Subjects will also become familiar with the PKG wearable device and the PD Diary. Prior to the Oral CD/LD Stabilization Period, subjects must experience an average daily "Off" time of at least 2.5 hours over 3 consecutive PD Diary days and a minimum of 2 hours each day to remain eligible for the study. The PD Diaries used for this evaluation must have at least 44 of the 48 daily entries completed. Subjects who fail to meet this requirement prior to V2 may repeat the PD Diary for 3 additional consecutive days during the Screening Period. If the "Off" time criterion is still not met, subjects must be screen failed.

Note: At V2 and prior to a subject's enrollment (V3), the investigator or designee must confirm eligibility criteria in EDC. The TA MD or designee (contact information on cover page) are readily available to discuss any questions the Investigator or designee may have regarding appropriateness of a specific subject or the criteria. The decision to enroll the subject is ultimately the investigator's responsibility.

In rare situations (e.g., genuine emergency, natural disaster, or for COVID-19-related disruptions), where screening cannot be completed within 60 days, the TA MD must be contacted for a case-by-case review and approval of potential rescreens.

Rescreened subjects will need to repeat all screening visits and screening procedures (except for the concordance test) and demonstrate that they still meet eligibility criteria and suitability to participate in the study prior to enrollment (V3).

Oral CD/LD Stabilization Period (Duration: 14 to 21 Days)

The Oral CD/LD Stabilization Period includes 3 visits: Visit 3 (V3), Visit 4 (V4), and Visit 5 (V5). V4 is optional at the investigator's discretion. All visits during the Oral CD/LD Stabilization Period will have a window of ± 2 days and subjects should be on the prescribed oral CD/LD IR regimen and concomitant PD medication as much as possible during the Oral CD/LD Stabilization Period until 12 hours prior to Visit 6 (V6) even if a visit is not occurring on the designated study day. The activities of the Oral CD/LD Stabilization Period are expected to take 14 to 21 days to accommodate scheduling and, when allowed, repeat assessments. The visits during this period are as follows:

- V3: All LD-containing medications (regardless of formulation), as well as those containing catechol-O-methyltransferase (COMT) inhibitors, will be converted to an equivalent amount of CD/LD IR. All COMT inhibitors will be suspended. All other concomitant PD medications (e.g., dopamine-agonists, monoamine oxidase B [MAO-B] inhibitors, safinamide, amantadine, istradefylline), although allowed, must remain unchanged until study completion, unless specific safety conditions dictate their modification. The new therapeutic regimen will consist of only CD/LD IR plus allowed non-LD-containing PD medications, if needed, and it should aim to achieve the best control of subjects' PD symptoms. After a brief clinical examination, subjects will be given their newly established therapeutic regimen of CD/LD IR tablets that subjects will initiate the morning of the following day. The CD/LD 25/100 mg IR tablets must be used whole; no split, crushed, or partial tablets may be used. Enrollment in the Oral CD/LD Stabilization Period and dispensing open-label CD/LD IR should be the last procedure of V3.
- Optional V4: Seven days after V3, the investigator will assess the subjects' PD symptoms and may adjust their CD/LD IR regimen, if needed. Concomitant PD medications must remain unchanged. If no adjustments to the CD/LD IR therapeutic regimen are needed for a full week after V3, subjects may skip the V4 assessments and proceed directly to the V5 assessments. If before or at V4, more adjustments are needed, then subjects will complete V4 assessments and return a week later for V5.
- V5 (Baseline Visit): Subjects will return to the clinic a week before randomization and complete V5 study activities. No further adjustments to the oral CD/LD IR may be made during V5. Subjects will be asked to keep their oral CD/LD IR therapeutic regimen unchanged until Visit 6 (V6, Day 1, Randomization Visit). Subjects (and caregivers, if applicable) will continue to be trained on the correct use of the PM-PDSC Pump Delivery System leading up to V5 and must again demonstrate at V5 the understanding and correct use of the delivery system, including the insertion of the cannula into the subject's abdomen, as assessed by the investigator or designee using the PM-PDSC Knowledge and Skills Checklist. Subjects who fail this requirement must be prematurely discontinued. V5 will be the Baseline Visit, unless otherwise indicated.

During the Oral CD/LD Stabilization Period, the CD/LD IR therapeutic regimen may be adjusted over the phone or in the office, both will be recorded as unscheduled visits if changes to the CD/LD IR therapeutic regimen occur between scheduled visits; however, no changes to the oral CD/LD IR therapeutic regimen should be made for at least 7 days before Day 1 (Randomization Visit, V6), unless for medical necessity (safety). Concomitant PD medications must remain unchanged.

Open-label CD/LD 25 mg/100 mg (25/100) IR tablets will be dispensed to subjects for use during the Oral CD/LD Stabilization Period.

Double-Blind Treatment Period (Duration: 85 Days)

The Double-Blind Treatment Period includes 8 study visits and has a duration of 12 weeks. All Double-Blind Treatment Period visits will have a window of ± 3 days with the exception of V6, which has a window of + 2 days, and V7, which has no window. Subjects should remain on the double-blind study drug as much as possible through D85/Premature Discontinuation Visit (V13) even if a visit is not occurring on the designated study day.

Randomization (Day 1 [V6]):

Subjects will arrive in the morning for their Randomization Visit in a practically defined "Off" state. No medications to treat PD symptoms should be taken for at least 12 hours before V6 to provide a clear picture of the untreated symptomatology of the disease.

After a clinical examination, continued study eligibility will be validated, which includes confirming the presence of at least 2 hours of "Off" time each day for 3 consecutive days on the PD Diary (PD Diaries must be completed prior to Day –1). The PD Diaries used for this evaluation must have at least 44 of the 48 daily entries completed. Subjects who do not meet this requirement must be prematurely discontinued from the study.

Subjects who meet all the eligibility criteria and continue to be suitable to participate in the study, per investigator's or designee's adjudication, will be randomized 1:1 into one of the 2 treatment arms:

- 24-hour/day CSCI of ABBV-951 plus oral placebo capsules for CD/LD IR

  OR

- 24-hour/day CSCI of placebo solution for ABBV-951 plus oral encapsulated CD/LD IR tablets

CSCI Optimization Phase (Day 1 [V6] through Day 29 [V11]):

Immediately following randomization on Day 1 (V6), subjects will begin the Double-Blind Treatment Period. In a blinded fashion, subjects will receive a dual loading dose on Day 1 with both oral study drug and study drug solution (see Table 1).

- For the oral loading dose, the number of study drug capsules will be identical to the number of CD/LD IR tablets taken as the first dose of the day at the end of the Oral CD/LD Stabilization Period.
- For the loading dose solution, the volume of study drug solution will be calculated based on the volume of ABBV-951 delivering an amount of LD equivalent to the number of CD/LD IR tablets taken as the first dose of the day at the end of the Oral CD/LD Stabilization Period. The loading dose solution will be delivered subcutaneously via the pump.

After the loading dose, subjects will start their infusion of blinded study drug solution and will concurrently receive blinded oral study drug.

Note: a loading dose is needed only on Day 1. This feature is then disabled on the PM-PDSC Pump for the duration of the study by setting the loading dose volume to 0.00 mL. The study design requires that every subject be switched to open-label LD/CD if the infusion has been interrupted for more than 1 hour in order to maintain subjects in the "On" state before restarting the continuous infusion and prevent unblinding.

During the CSCI Optimization Phase, only changes to the CSCI will be permitted; oral study drug and allowed concomitant PD medications must be maintained at the already optimal and stabilized pre-randomization dose and schedule. Changes to the concomitant PD medications are not allowed, unless necessary for safety reasons.

During the CSCI Optimization Phase, subjects will be evaluated on Day 2 (V7), Day 8 (V8), Day 15 (V9), Day 22 (V10) (optional), Day 29 (V11), and any intervening days as needed (recorded as unscheduled visits). During each visit, the investigator will assess the subject's PD symptoms and may adjust the subject's CSCI infusion rate based on the subject's clinical response. 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.

Subjects will be instructed to record, in the Subject Dosing Diary, all oral CD/LD IR tablets taken as rescue medication during the Double-Blind Treatment Period (i.e., not only 3 consecutive days prior to study visits). Subjects will also track infusion sites in the Infusion Site Rotation Tool to help guide their rotation pattern and prevent overuse of an infusion site area throughout the Double-Blind Treatment Period.

During the CSCI Optimization Phase, study visits will occur as follows:

- Day 1 (V6) Randomization
- Day 2 (V7)
- Day 8 (V8)
- Day 15 (V9)
- Optional Day 22 (V10) – If the investigator determines no adjustments to the infusion rate are needed through phone contact, subjects may skip V10.
- Day 29 (V11)

Maintenance Phase (After Day 29 [V11] through Day 85 [V13]):

After Day 29 (V11), subjects will begin the Maintenance Phase and should maintain stable treatment regimens of blinded study drug solution and blinded oral study drug as well as other concomitant medications, including any PD medications that are still being administered. Dose adjustments of non-study-drug medications may be made only if considered medically necessary (e.g., management of dyskinesia), in the investigator's opinion. In case of sudden deterioration of clinical condition, rescue tablets of CD/LD IR may be taken.

Subjects will be instructed to record, in the Subject Dosing Diary, all oral CD/LD IR tablets taken as rescue medication during the Double-Blind Treatment Period (i.e., not only 3 consecutive days prior to

study visits). Any changes to medications, including the optimized randomized regimens, should be recorded in the electronic case report form (eCRF).

During the Maintenance Phase, study visits will occur as follows:

- Day 57 (V12)
- Day 85 (V13) or premature discontinuation

Dermatologic Assessments

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 and/or caregiver training and adherence to proper techniques is 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.[1] Most are mild or moderate in severity and generally self-resolving, with or without therapy. 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 in order to minimize the risk of infections.

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 3.7 of the Operations Manual in 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 the photographs. In rare situations where an assessment or visit cannot be completed onsite due to an extenuating event (e.g., genuine emergency, natural disaster, 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 after 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.

Study Drug Regimens during the Double-Blind Treatment Period

Subjects will receive both a 24-hour/day CSCI of the blinded study drug solution and blinded oral study drug. The starting continuous infusion rate will be calculated based on the total amount of LD that the subject receives during the waking time at the end of the Oral CD/LD Stabilization Period and a conversion algorithm based on the pharmacokinetic characteristics of ABBV-951. Subjects will receive the blinded oral study drug that will match, in number of tablets and dosing frequency, the therapeutic schedule that was achieved during the Oral CD/LD Stabilization Period.

The investigator may adjust the prescribed infusion rate only during the CSCI Optimization Phase. Oral study drug must remain unchanged for the entire Double-Blind Treatment Period.

Rescue Medication

All subjects will receive open-label CD/LD IR tablets for use as rescue medication. Once the Double-Blind Treatment Period has been initiated, rescue tablets should only be used in the case of a serious medical need, such as rapid deterioration of motor symptoms. Rescue doses during the Double-Blind Treatment Period are the only doses taken during the study that allow the administration of half tablets of CD/LD IR. Subjects will be instructed to record, in the Subject Dosing Diary, all oral CD/LD IR tablets taken as rescue medication during the Double-Blind Treatment Period (i.e., not only 3 consecutive days prior to study visits).

Post-Treatment Activities

Subjects who complete the study may be eligible for the open-label extension Study M20-098 in which all subjects will receive a 24-hour/day CSCI of ABBV-951 at individually optimized therapeutic dose levels.

There are no post-treatment activities except for subjects who prematurely discontinue study participation. See Section 5.7 for additional information:

Study Completion

Once all randomized subjects complete the study, or prematurely discontinue, the database will be locked. The blind will be broken and the data will be analyzed by the sponsor according to a prespecified statistical analysis plan (SAP).

4.2 Discussion of Study Design

Choice of Control Group

Carbidopa/levodopa remains the standard of care for PD.

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 aPD who report motor fluctuations that are inadequately controlled by their current PD treatment and who experience a daily average of at least 2.5 hours of "Off" time (with a minimum of 2 hours each day) as assessed by PD diaries completed in 3 consecutive days prior to V2.

Rationale for Selection of Therapeutic Dose Range

It is recognized that the treatment of PD is highly individualized; both the treatments administered and their doses are often customized, based on the patients' signs and symptoms and their response to medication. This results in a wide distribution of therapeutic doses, in clinical practice and in clinical trials.

Previous data from LCIG suggest that LD doses could range from less than 700 mg/day to approximately 4260 mg/day, over a 24-hour daily treatment period. This is equivalent to approximately 1000 to 6000 mg LDP per day, which was selected as the range of possible ABBV-951 daily doses for the study.

Loading Dose for Study Drug Solution

The volume of the loading dose for study drug solution will be calculated based on the volume of ABBV-951 delivering an amount of LD equivalent to the number of CD/LD 25/100 IR tablets taken as the first dose of the day at the end of the Oral CD/LD Stabilization Period, as presented in Table 1. The loading dose solution will be delivered subcutaneously via the pump on Day 1 only. After delivery of the loading dose on Day 1, this function will be disabled by the investigator or designee for the remainder of the study by adjusting the loading dose volume to 0.00 mL.

Table 1. Infusion Loading Dose Determination

LD from First Morning Dose of CD/LD IR at End of Stabilization Period (mg)	Infusion Loading Dose[a] (mL)	Approximate Duration of Loading Dose (minutes)
100	0.6	6
200	1.1	12
300	1.6	18
≥ 400	2.2	24

CD/LD = carbidopa/levodopa; IR = immediate release; LD = levodopa; LDP = levodopa phosphate

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

Continuous Infusion Rates

ABBV-951 or placebo solution will be delivered continuously (24 hours/day) via an infusion set connected to a pump designed for ambulatory use. Each subject's starting continuous infusion rate will be calculated based on the subject's stabilized oral CD/LD IR therapy at the end of the Oral CD/LD Stabilization Period and an algorithm developed following a combination of pharmacokinetic and clinical considerations from ABBV-951 Phase 1 studies.

Based on the total amount of oral LD that the subject receives during the 16-hour typical waking time at the end of the Oral CD/LD Stabilization Period, the starting infusion rate for ABBV-951 or placebo solution should be selected from Table 2, using the rates under the column heading "Starting Infusion Rate." These starting continuous infusion rates are estimated for the mid-point of the LD intervals provided.

Table 2. Starting Infusion Rates Determination and Limits on Continuous Infusion Rate During Study

Daily LD from CD/LD IR at End of Stabilization Period (mg/16 hr)[a]	Starting Infusion Rate[b] (mL/hr)
< 500	0.16
500	0.18
600	0.20
700	0.24
800	0.27
900	0.30
1000	0.34
1100	0.37
1200	0.40
1300	0.44
1400	0.47
1500	0.50
1600	0.54
1700	0.57
1800	0.60
1900	0.64
2000	0.67
2100	0.70
2200	0.74

Daily LD from CD/LD IR at End of Stabilization Period (mg/16 hr)[a]	Starting Infusion Rate[b] (mL/hr)
2300	0.78
2400	0.81
2500	0.84
2600	0.88
2700	0.91
2800	0.94
2900	0.98
3000	1.00
≥ 3100	1.04[c]

CD/LD = carbidopa/levodopa; hr = hour; IR = immediate release; LD = levodopa; LDP = levodopa phosphate

a. Do not subtract the first morning dose.

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

c. AbbVie Therapeutic Area Medical Director (TA MD) to be contacted; see bolded text at the end of Section 4.2.

CSCI Optimization

The ABBV-951 or placebo solution infusion rate may be adjusted at the investigator's discretion only during the CSCI Optimization Phase.

Achieving and maintaining an optimal therapeutic response for the individual subject 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. The infusion pump allows the infusion rate to be increased or decreased by multiples of 0.01 mL/hour which, for the ABBV-951 solution, correspond to approximately 1.7 mg LD/hour. The minimum infusion rate must be at least 0.15 mL/hour, and the maximum infusion rate cannot exceed 1.04 mL/hour. Under no circumstances can infusion rates be set below 0.15 mL/hour or above 1.04 mL/hour.

Conversion Algorithm

The conversion algorithm was created taking into consideration the molecular weight of LDP, drug product concentration, pharmacokinetic data, and clinical considerations from ABBV-951 Phase 1 studies.

Assumptions Used to Generate the Algorithm

From pharmacokinetic studies, a conversion factor of oral levodopa to LDP was determined to be 1.41 based on differences in molecular weight. One milliliter of the ABBV-951 drug product used in this study contains 240 mg of LDP and 12 mg of CDP.

Most PD patients are treated with oral PD medications during their waking time (typically 16-hour/day treatment period). Once the amount of LDP needed over the 16-hour period has been calculated, it is divided by 240 mg to determine the number of milliliters needed over the 16-hour period, and then

divided over 16 hours to establish the hourly infusion rate. ABBV-951 is meant to be administered over 24 hours daily, so once the hourly infusion rate is established, the treatment period is extended for the additional 8 hours to account for nighttime treatment.

Note: Should the daily LD from CD/LD IR at the end of the Oral CD/LD Stabilization Period for a subject be estimated to be ≥ 3100 mg, which is equivalent to > 6000 mg LDP/day (i.e., requiring an infusion rate > 1.04 mL/hour), the investigator should contact the AbbVie TA MD to discuss the subject's levodopa responsiveness, clinical status, and subsequent study drug dosing. Under no circumstances are infusion rates > 1.04 mL/hour allowed.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

All subjects will be evaluated to ensure they meet the eligibility criteria during the Screening Period, prior to entering the Oral CD/LD Stabilization Period, and prior to randomization on Day 1 (V6). Subjects must meet all eligibility criteria prior to the Oral CD/LD Stabilization Period and the administration of open-label CD/LD IR tablets at V3. Subjects must continue to meet these eligibility criteria prior to randomization (V6) and administration of blinded study drug.

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 male or female, 30 years of age or older at Screening (V1).
- 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 V1.[a]
- 6. Subject has normal cognitive function (Mini-Mental State Examination [MMSE] score of 24 or greater).
- 7. Subject is considered to be a suitable candidate to receive ABBV-951 and subject (or caregiver, if applicable) demonstrates the understanding and correct use of the delivery system, including the insertion of the cannula into the subject's abdomen, as assessed by the investigator or designee during the Screening Period[b] and at V5.[c]

Disease Activity

- 8. Subject must have a diagnosis of levodopa-responsive idiopathic PD and the total daily dose of LD equivalents from LD-containing medication and COMT inhibitors must be ≥400 mg.
- 9. Subject must have recognizable/identifiable "Off" and "On" states (motor fluctuations) as established through investigator observation and confirmed by PD Diary entries recorded during the concordance test performed during the Screening Period.
- 10. Subject must be judged to be inadequately controlled by current therapy in the investigator's opinion and experience a minimum daily average of 2.5 hours of "Off" time (with a minimum of 2 hours of "Off" time each day) as assessed by PD Diary for 3 consecutive days prior to V2[d] and maintain at least 2 hours of "Off" time each day for 3 consecutive days before V6 (Randomization Visit).[e]
- 11. Subject has not received deep brain stimulation, CD/LD enteral suspension, or any other PD medication as continuous daily infusion, whether commercially available or investigational. Previous exposure to ABBV-951 is not allowed.

Subject History

- 12. 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.[f]
- 13. Subject does not have a recent (within 6 months prior to screening [V1]) history of drug or alcohol abuse that could preclude adherence to the protocol in the investigator's opinion.
- 14. Subject does not have significant suicidal ideation currently or within 1 year prior to screening (V1) as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the C-SSRS, or any history of suicide attempts within the last 2 years.
- 15. 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.
- 16. 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.
- 17. 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.
- 18. Subject agrees to receive CD/LD IR and has no 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).
- 19. 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 Screening (V1).

- 20. 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

- 21. If female of childbearing potential, subject must have a negative serum pregnancy test at V1, and a negative urine pregnancy test at V3 prior to start of the Oral CD/LD Stabilization Period and a negative urine pregnancy test on Day 1 (V6) prior to randomization. Female subjects of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2) at V1 do not require pregnancy testing.
- 22. If female, subject must be either **postmenopausal**, OR permanently **surgically sterile** OR for women of childbearing potential practicing at least 1 protocol-specified **method of birth control** that is effective from V3 through at least 30 days after the end of study drug administration (end of Double-Blind Treatment Period).
- 23. If male and **sexually active with female partner(s) of childbearing potential**, subject must agree to practice protocol-specified contraception from V3 through 30 days after the end of study drug administration.
- 24. 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 study drug administration.
- 25. If male, subject is not considering fathering a child or donating sperm during the study or within 30 days after the end of study drug administration.

Concomitant Medications

- 26. Subject has not received an investigational product within a time period equal to 5 half-lives, if known, or within 6 weeks, whichever is longer, prior to randomization.

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 retest for vitamin B_{12} is allowed during the Screening Period without repeating other screening procedures.

b. *Subjects who do not meet the demonstration of understanding and correct use of the delivery system criterion at V2 may repeat the assessment once (without repeating other screening procedures) at an unscheduled visit prior to the start of the Oral CD/LD Stabilization Period (V3). If the criterion is still not met, subjects must be screen failed.*

c. *Subjects who do not meet the demonstration of understanding and correct use of the delivery system criterion at V5 must be prematurely discontinued from the study.*

d. *Subjects must experience an average daily "Off" time of at least 2.5 hours over 3 consecutive PD Diary days and a minimum of 2 hours each day prior to V2 to remain eligible for the study. The PD Diaries used for this evaluation must have at least 44 of the 48 daily entries completed. Subjects who fail to meet this requirement prior to Visit 2 may repeat the PD Diary for 3 additional consecutive days prior to V3. If the "Off" time criterion is still not met, subjects must be screen failed.*

e. *Subjects who do not meet the required minimum of at least 2 hours of "Off" time each day for 3 consecutive days before V6 (Randomization Visit) must be prematurely discontinued from the study. The PD Diaries used for this evaluation must have at least 44 of the 48 daily entries completed.*

f. *Subjects with evidence of transient skin conditions such as recent sunburn or open wound that resolved prior to V6 are eligible for randomization.*

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 meeting 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 (FSH) 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 the study and for at least 30 days after the end of study drug administration. Females of childbearing potential must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to V6.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 Days prior to V6.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).

- Intrauterine hormone-releasing system (IUS).
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice 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).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Male subjects, including those who have undergone a successful vasectomy, who are sexually active with a female partner of childbearing potential must agree to the following from V3 through at least 30 days after the end of study drug administration:

- Use condoms.

  AND

- His female partner(s) must also use at least 1 of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to V6.
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to V6.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - IUD.
  - IUS.

5.3 Prohibited Medications and Therapy

The medications listed in Table 3 are prohibited during the Oral CD/LD Stabilization Period and the Double-Blind Treatment Period.

Table 3. Prohibited Medications

Apomorphine[a]
Levodopa-carbidopa intestinal gel (LCIG)/carbidopa-levodopa enteral suspension (CLES)
Dopamine-depleting agents (e.g., reserpine, tetrabenazine, amphetamines)
MAO-A inhibitors and non-selective MAO inhibitors[b]
Ergot dopamine agonists (e.g., lisuride, bromocriptine, cabergoline)
Dopamine antagonist or partial agonist, first generation antipsychotics, or antiemetic medications that interact with brain dopamine receptors (e.g., fluphenazine, loxapine, perphenazine, thiothixene, haloperidol, metoclopramide, aripiprazole, asenapine)
Oral and/or inhaled medications containing levodopa[c]
COMT inhibitors (e.g., entacapone, tolcapone, opicapone)[d]

CD/LD = carbidopa/levodopa; COMT = catechol-O-methyltransferase; IR = immediate release; MAO-A = monoamine oxidase A

a. Apomorphine injection is allowed as a rescue medication during the Screening Period; it must be discontinued prior to starting Oral CD/LD Stabilization Period study drug and is prohibited for the remainder of the study.

b. 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.

c. Allowed during the Screening Period; must be discontinued prior to starting Oral CD/LD Stabilization Period study drug and is prohibited for the remainder of the study. CD/LD IR provided for the study is allowed in case of serious sudden medical need as rescue medication.

d. Allowed during the Screening Period; must be discontinued prior to starting Oral CD/LD Stabilization Period study drug and is prohibited for the remainder of the study.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from 30 days prior to 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 sponsor contact or emergency medical contact. Information regarding potential drug interactions with ABBV-951 is located in the ABBV-951 Investigator's Brochure.[1]

With the exception of the Oral CD/LD Stabilization Period and the CSCI Optimization Phase, subjects should remain on stable PD medication for the duration of the study, unless medically needed.

All subjects will be provided with oral CD/LD 25/100 IR tablets in case rescue therapy is needed during the Double-Blind Treatment Period. Once blinded study drugs have been initiated, rescue tablets should only be used in the case of a serious medical need, such as rapid deterioration of motor symptoms. The subject should be instructed to record, in the Subject Dosing Diary, all oral CD/LD IR tablets taken as rescue medication during the Double-Blind Treatment Period (i.e., not only 3 consecutive days prior to study visits).

The following concomitant (Table 4) and rescue (Table 5) medications are allowed:

Table 4. Allowed Concomitant Medications/Therapy

Allowed Concomitant Medications/Therapy
Non-ergolinic dopamine agonists[a] (e.g., pramipexole, ropinirole, rotigotine)
Selective MAO-B inhibitors (e.g., rasagiline, selegiline)
Amantadine (IR and ER formulations)
Safinamide
Istradefylline

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

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

Table 5. Allowed Rescue Medications/Therapy

Rescue Concomitant Medications/Therapy	Comments/Notes
CD/LD 25/100 IR	Allowed as rescue therapy (e.g., in the event of a serious medical need, such as rapid deterioration of motor symptoms). Half tablets are allowed.

25/100 = 25 mg/100 mg; CD/LD = carbidopa/levodopa; IR = immediate release

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 Questions 4 or 5 on the C-SSRS; these subjects should be referred for appropriate follow-up care.

For subjects to be considered 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.

The investigator should contact the sponsor emergency medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

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

If a pump malfunction causes blinded study drug infusion to stop, subjects must simultaneously stop administration of blinded oral study drug capsules and contact the site. Subjects should take open-label CD/LD IR tablets at the regimen established during the Oral CD/LD Stabilization Period until infusion of blinded study drug solution can be resumed, at which time oral dosing of blinded study drug capsules should also be resumed. Half tablets of CD/LD IR are not allowed in this situation.

A subject's blinded study drug treatment may need to be temporarily suspended for medical reasons (e.g., illness, hospitalization). If such a situation occurs, subjects who experience a suspension up or equal to 3 days in duration may be reinitiated on blinded study drug at the investigator's discretion. If blinded study drug is suspended for more than 3 days, approval from the AbbVie TA MD is required prior to blinded study drug being restarted.

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

If a subject prematurely discontinues study drug during the open-label Oral CD/LD Stabilization Period, a follow-up visit or phone call will be completed 30 days after the last dose of study drug, if the subject is willing, to ensure all treatment-emergent AEs/SAEs have been resolved.

If a subject prematurely discontinues blinded study drug, the procedures outlined for V13 (also the Premature Discontinuation Visit for the Double-Blind Treatment Period) should be completed as soon as possible, preferably within 2 weeks. To minimize missing data for efficacy and safety assessments, subjects will continue study participation to be followed for all regularly scheduled visits, unless subjects have decided to discontinue study participation entirely. Subjects should be advised on the continued scientific importance of their data even if they prematurely discontinue treatment with blinded study drug. If a subject discontinues study participation during the Double-Blind Treatment Period or

completes the study but will not participate in the extension Study M20-098 and is willing, a follow-up visit or phone call 30 days after the end of study drug administration will be completed to ensure all treatment-emergent AEs/SAEs have resolved. If a subject prematurely discontinues study participation and withdraws informed consent, no further attempt to contact the subject will be made.

Only subjects who complete the 12-week double-blind study drug and study visits through V13 are eligible for the extension Study M20-098. For subjects who enroll in the extension study, Study M15-736 activities end with V13 and there is no follow-up visit or phone call.

5.8 Study Drug and Study Devices

The investigational product in this study consists of ABBV-951 (solution for infusion) and study devices. Additional study drug includes placebo for ABBV-951 (solution for infusion), the comparator drug (CD/LD IR), placebo for the comparator drug, and open-label CD/LD IR. Although this is not an investigational device trial and some of the devices are approved in some countries in which the study will be conducted, they will be labeled for investigational use.

Information for the ABBV-951 formulation and devices to be used in this study is presented in Table 6 and Table 7, respectively.

Table 6. Identity of Study Drug

Study Period	Study Drug	Dosage Form	Deliverable Content	Manufacturer
Oral CD/LD Stabilization Period (open-label) and rescue during Double-Blind Treatment Period	CD/LD[a]	Tablet/Oral	25/100 mg	Generic manufacturer
Double-Blind Treatment Period	ABBV-951 12/240 mg/mL (CDP4'/LDP4') S.INF. 10 mL vial	Solution for infusion/SC	120 mg/2400 mg (CDP4'/LDP4')	AbbVie
	Placebo solution for ABBV-951 10 mL vial	Solution for infusion/SC	NA	AbbVie
	CD/LD[a]	Over-encapsulated tablet/Oral	25/100 mg	Generic manufacturer; over encapsulation by AbbVie
	Placebo for CD/LD IR	Capsule/Oral	NA	AbbVie

CD/LD = carbidopa/levodopa; CDP4' = carbidopa phosphate four prime; IR = immediate release; LDP4' = levodopa phosphate four prime; S.INF. = solution for infusion; SC = subcutaneous

a. All CD/LD tablets are immediate release.

Table 7. Identity of Study Devices

Description	Usage	Manufacturer	Model Number
Infusion Pump and its accessories	Delivery of ABBV-951 or placebo solution	Phillips - Medisize Corporation	Phillips-Medisize - Parkinson's Disease Subcutaneous (PM-PDSC) Reference # 70000042
Syringe without needle	Delivery of ABBV-951 or placebo solution	B.Braun Medical Inc.	Omnifix™ syringe, luer lock, 10 mL; B Braun Medical reference #: 4617100V-02 (US)
Infusion Set	Delivery of ABBV-951 or placebo solution	Unomedical A ConvaTec Company	Neria™ Guard infusion set, 6 mm cannula, 60 cm tubing; Unomedical reference #: 704060-5226 USA (US) Neria™ Guard infusion set, 9 mm cannula, 60 cm tubing; Unomedical reference#: 704060-5229 USA (US)
Vial adapter	Facilitates transfer of ABBV-951 or placebo solution to syringe/reservoir	West Pharmaceutical Services	West Item ID: 36098056; Medimop Cat #: 8073005

US = United States
Note: All devices described above are part of the PM-PDSC Delivery System.

Selection of Doses in the Study

Open-label CD/LD 25/100 IR tablets will be taken orally over 24 hours and each subject's dose will be individually optimized for a 24-hour daily treatment during the Oral CD/LD Stabilization Period.

- The oral doses of CD/LD IR tablets and other permitted PD medications should be adjusted to achieve a stable clinical response for the individual subject, with the goal of 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.

A CSCI of ABBV-951 or placebo solution (double-blind) will be administered subcutaneously during the Double-Blind Treatment Period, delivered 24-hour/day via an infusion set connected to a pump designed for ambulatory use.

- Each subject's starting infusion rate will be calculated based on the dose of total LD that the subject receives at the end of the Oral CD/LD Stabilization Period, normalized to a 16-hour waking time, and an algorithm validated with Phase 1 studies.
- Infusion rates will range from 0.15 to 1.04 mL/hour.
- The infusion rate may be adjusted to an optimal 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 troublesome dyskinesia.

Encapsulated CD/LD 25/100 IR tablets or placebo capsules (double-blind) will be taken orally 24-hour/day and will follow the same administration schedule used for the oral CD/LD 25/100 IR at the end of the Oral CD/LD Stabilization Period.

Subject dosing will be recorded in a Subject Dosing Diary for 3 consecutive days prior to any study visit as specified in the study activity schedule in Appendix D. In case of sudden deterioration of clinical condition, rescue tablet(s) of CD/LD IR may be taken. Subjects will be instructed to record, in the Subject Dosing Diary, all oral CD/LD IR tablets taken as rescue medication during the Double-Blind Treatment Period (i.e., not only 3 consecutive days prior to study visits).

If a subject is unable to come to the study site to pick up study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix F for details on DTP shipment of study drug.

Device

The Phillips-Medisize Parkinson's Disease Subcutaneous (PM-PDSC) pump comes in a package that includes the pump, a pump carrying accessory, rechargeable batteries, and charging station. Detailed instructions for use (IFUs) will be provided to clinical study personnel for programming the pump, to subjects for using the PM-PDSC Pump Delivery System to administer the solution for infusion, and to subjects for preparing study drug. Detailed IFUs will also be provided to subjects for using carrying accessories, the infusion set, the vial adapter, and the battery charging station.

The investigator or designee is required to disable the alternative infusion rates (Low and High infusion rates) and extra dose functionalities available on the PM-PDSC pump for Study M15-736. These functionalities are disabled by programming the Low and High rates to be the same as the Base rate and setting the extra dose volume as "0.00." After delivery of the loading dose on Day 1, this pump function will also be disabled by the investigator or designee for the remainder of the study by adjusting the loading dose volume to 0.00 mL.

The site is required to hand write the expiry date generated by the IRT system on the pump label when the pump is dispensed to a subject.

Treatments Administered

Oral CD/LD Stabilization Period (V3, optional V4, V5)

Beginning the morning after V3, subjects will take their regimen of CD/LD 25/100 IR tablets, converted from all LD-containing oral medications and COMT inhibitors, as specified in Table 8, in order to standardize their dosing regimen and be compatible with the oral study drug to be taken during the Double-Blind Treatment Period.

Table 8. Guidance for Conversion from LD-Containing Medications to CD/LD IR

Medication	Multiplying Factors to Calculate LD Equivalents
Immediate-release levodopa (e.g., Sinemet IR)	No adjustment needed (e.g., multiply by 1).
Sustained-release levodopa (e.g., Sinemet CR)	For subjects taking sustained-release levodopa, **multiply** their daily dose of sustained-release levodopa **by 0.75** to obtain their LD IR equivalent.
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 LD IR equivalent.

Rytary Dose Range (mg)	Conversion Ratio (Rytary to LD Equivalent)
0 – 855	**0.42**
856 – 1755	**0.48**
1756 – 2340	**0.56**
≥ 2341	**0.67**

Medication	Correction Factor for COMT inhibitors
COMT inhibitors: entacapone (e.g., Comtan or Stalevo) or tolcapone (Tasmar) or opicapone (Ongentys)	If subjects are taking tolcapone, entacapone, or opicapone concomitantly, the sum of all LD equivalents calculated thus far must be **multiplied by 1.33**. Note: The levodopa dose contained in Stalevo counts as IR.

CD = carbidopa; CR = sustained release; COMT = catechol-O-methyltransferase; IR = immediate release; LD = levodopa

Note: The conversion factors provided are based on data from the literature.[2,3]

The correction factor must be applied to the sum of LD equivalents calculated from all levodopa-containing formulations. The levodopa contained in combined CD/LD/entacapone formulations counts as immediate-release and needs to be added to the LD equivalents from all other sources of levodopa before the sum is multiplied for the COMT inhibitors corrective factor.

The levodopa amount from all levodopa-containing formulations taken during the 16-hour waking time of the day should be converted to LD equivalents (i.e., equivalent amount of CD/LD IR) using the appropriate multiplying factor and summed. Do not consider nighttime dosing or additional supplemental levodopa, rescue or herbal therapies for this calculation. If COMT inhibitors are taken concomitantly, a correction factor should be applied to the sum of LD equivalents.

Subjects will continue to take their other allowed concomitant PD medications (e.g., dopamine agonists, MAO-B inhibitors), which must remain unchanged. At this time, COMT inhibitors will be suspended. During this 14- to 21-day period, the CD/LD IR regimen will be optimized to achieve the best control of the subject's motor symptoms as possible.

The oral CD/LD 25/100 mg IR tablet medication schedule may accommodate nighttime treatment. The CD/LD 25/100 mg IR tablets must be used whole; no split, crushed, or partial tablets may be used.

Randomization (Day 1 [V6])

The morning of randomization, subject will arrive in a practically defined "Off" state (i.e., no PD medications including CD/LD IR, dopamine agonists, MAO-B inhibitors, etc., for at least 12 hours before V6). At the beginning of the visit, after the study personnel verifies that the subjects continue to meet the study selection criteria, subjects will be randomized 1:1 into one of 2 treatment arms:

- 24-hour/day CSCI of ABBV-951 plus oral placebo capsules for CD/LD IR

  OR

- 24-hour/day CSCI of placebo solution for ABBV-951 plus oral encapsulated CD/LD IR tablets

Subjects will receive their study drugs, pump, infusion system, and ancillary devices, and immediately begin the CSCI Optimization Phase after completion of the pre-dose assessments, as indicated in Appendix D.

CSCI Optimization Phase (V6, V7, V8, V9, Optional V10, V11)

- In a blinded fashion, subjects will receive a dual loading dose with both oral study drug and study drug solution.
- For the oral loading dose, the number of study drug capsules will be identical to the number of CD/LD IR tablets taken as the first dose of the day at the end of the Oral CD/LD Stabilization Period.
- For the loading dose solution, the volume of study drug solution will be calculated based on the volume of ABBV-951 delivering an amount of LD equivalent to the number of CD/LD IR tablets taken as the first dose of the day at the end of the Oral CD/LD Stabilization Period, and will be delivered subcutaneously via the pump (Table 1).
- After the dual loading doses, subjects will start the continuous infusion of blinded study drug solution. The infusion rate of ABBV-951/placebo solution will be calculated based on the subject's LD dose over the 16-hour/day waking treatment period at the end of the Oral CD/LD Stabilization Period and selected from Table 2.
- Concurrently, subjects will receive blinded oral study drug. Their CD/LD IR tablets will be replaced with study-provided capsules, which could contain active CD/LD 25/100 mg IR or placebo. The oral capsules will be taken at the same schedule as determined at the end of the Oral CD/L.
- After delivery of the loading dose on Day 1, this pump function will be disabled by the investigator or designee for the remainder of the study by adjusting the loading dose volume to 0.00 mL.
- The CSCI Optimization Phase will allow for modification of the infusion rates for study drug solution for both treatment arms, if needed. The minimum infusion rate must be at least 0.15 mL/hour, and the maximum infusion rate cannot exceed 1.04 mL/hour. During this phase, modification of the oral study drug or concomitant PD medications will not be allowed.
- The pump will be programmed by the site per the pump IFU for clinical study personnel.
- After 4 weeks, the subject will enter the Maintenance Phase.

Maintenance Phase (Day after V11 through V13)

- Subjects should maintain a stable treatment regimen of their optimized randomized regimens and other concomitant medications, including any allowed PD medications that are still being administered.
- Adjustments of concomitant PD medications will not be allowed unless considered medically necessary, for safety reasons.
- At any time, subjects may take open-label CD/LD IR tablet(s) as rescue medication to address immediate, serious medical needs, such as the rapid deterioration of motor symptoms. Subjects will be instructed to record, in the Subject Dosing Diary, all oral CD/LD IR tablets taken as rescue medication during the Double-Blind Treatment Period.

CSCI Optimization Phase and the Maintenance Phase

The ABBV-951/placebo solution will be self-administered by the subject or by a caregiver (if applicable) using study devices (i.e., infusion set connected to an infusion pump) indicated for subcutaneous delivery. The PM-PDSC Pump Delivery System will need to be loaded with the study drug solution with the same cadence every day (e.g., every morning for subjects who require 1 vial per day; after breakfast and before dinner, or every 12 hours, for subjects who require 2 vials per day; before breakfast, after lunch and before bedtime, for subjects who require 3 vials per day). Study drug solution will be loaded into a syringe that will then be placed in the pump. When vials are changed, depending on how long the infusion set has already been in use, subjects may need to either change just the syringe (using a new vial and vial adapter) or change the syringe and use a new infusion set (i.e., infusion set tubing and insertion device/cannula pad, which could be used for up to 3 consecutive days when the drug is infused continuously).

The infusion should be administered at least 5 cm (or 2 inches) away from the umbilicus and 2.5 cm (or 1 inch) from the previous infusion site. Infusions should also be administered at least 5 cm (2 inches) away from areas of scarred or hardened tissue or stretch marks, skin folds or creases where the body naturally bends, or areas where clothing might cause irritation (e.g., near the beltline).

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 set and the infusion site (area of the skin where the subcutaneous cannula is inserted) may be left unchanged for up to 3 days when the drug is infused continuously. This includes maintaining the same infusion set when using a new vial; however, a new vial adapter and a new syringe are required any time a new vial is used.

Note: 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. Each time the infusion site is rotated, a new infusion set is to be used.

Subjects will track infusion sites in the Infusion Site Rotation Tool to help guide their rotation pattern and prevent overuse of an infusion site area throughout the Double-Blind Treatment Period.

Infusion Interruption

If the infusion is interrupted and study drug is not administered for more than 1 hour, subjects should replace the infusion set and rotate the infusion site before resuming study drug administration. No action is needed if the infusion pump is disconnected and study drug is not administered for less than 1 hour (such as when changing syringes).

Under no circumstance can a single syringe be used for longer than 24 hours.

In the event of an infusion pump malfunction or other event that prevents delivery of blinded study drug solution for more than 1 hour, the time period during which study drug was not delivered will be recorded by the site, in the electronic data capture system. Subjects should simultaneously stop administration of blinded oral study drug capsules and begin taking open-label CD/LD IR tablets at the regimen (same number of tablets and frequency of dosing as the oral study drug capsules) established during the Oral CD/LD Stabilization Period until infusion of the blinded study drug solution can be resumed. Half tablets of CD/LD IR are not allowed in this situation. The subject should call the clinical study personnel, so that the subject 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). When the infusion is resumed, the restart time will be recorded to the minute; no changes to the Base infusion rate are permitted; the subject will stop taking open-label CD/LD IR tablets and will resume oral dosing of blinded study drug capsules.

Note: Switching subjects to open label LD/CD if the infusion has been interrupted for more than 1 hour maintains subjects in the "On" state before restarting the continuous infusion and minimizes the risk of unblinding.

If the study drug infusion cannot 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.

Blinding

All study drug during the Oral CD/LD Stabilization Period and the CD/LD IR used as rescue medication during the Double-Blind Treatment Period will be open-label.

Study drug for the Double-Blind Treatment Period will be blinded. Since ABBV-951 and placebo solution may not appear identical, the following measures are required:

- All AbbVie personnel with direct oversight of the conduct and management of the study, with the exception of the AbbVie Drug Supply Management Team, will remain blinded to the treatments.
- Every effort will be made to ensure study personnel, including the treating investigator, remain blinded. Study sites will have at least 3 distinct personnel with non-overlapping roles:
    - Study site personnel who provide the study drug (e.g., pharmacist or study nurse): these personnel must be different from the personnel who assess subjects for the safety and efficacy endpoints. This staff member should be the designated contact to address any subject questions related to the study drug solution. IP accountability should also be limited to this site staff member.

- Treating investigators: the treating investigator or designee should assess AEs, manage the device (including dose changes during the CSCI Optimization Phase), perform safety assessments, and control the use of rescue medications.
- Efficacy raters: study sites will use a separate rater (i.e., other than the site personnel who provide study drug or the treating investigator) to perform all in-person efficacy assessments (i.e., MDS-UPDRS). The infusion tubing should be completely hidden from view and remain hidden while the efficacy rater sees subjects. Subjects (and caregivers, if applicable) should be instructed not to discuss other study-related matters with the efficacy rater.

  Note: after the CSCI Optimization Phase starts, if the treating investigators or efficacy raters train subjects on the use of the PM-PDSC Pump Delivery System, every effort must be made to maintain the blind, including using training pumps for demonstration/training purposes.

- Subjects (and caregivers, if applicable) will remain blinded to the subject's treatment throughout the study.
- CD/LD IR tablets are over-encapsulated and identical in appearance to the placebo capsules. The over-encapsulated CD/LD IR tablets and placebo capsules are packaged identically.
- ABBV-951 solution for infusion and the placebo solution for infusion will be packaged identically.

All staff may have access to interactive response technology (IRT); however, treating investigators and efficacy raters should not be exposed to IP contents within the kits.

To prevent functional unblinding, the following additional measures are required:

- The alternative infusion rates (Low and High infusion rates) and extra dose functionalities designed for the PM-PDSC pump will be disabled.
- Central raters will be used for the administration and assessment of the Parkinson's Disease Sleep Scale-2 and the Parkinson's Disease Questionnaire-39. Central raters will not have access to the results of other study assessments or subjects' medical records and will not participate in the care or management of subjects.

The interactive response technology (IRT) will provide access to unblinded subject treatment information in the event of a medical emergency that requires unblinding. The investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary that warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system via the Unblinding transaction that is available only to the investigator, sponsor medical monitor, and sponsor pharmacovigilance lead. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email. For country-specific phone numbers, please see the following website: https://www.endpointclinical.com/contact/.

In the event that the blind is broken before notifying the AbbVie TA MD, the AbbVie TA MD should be notified within 24 hours of the blind break. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

Packaging and Labeling

CD/LD IR open-label tablets will be supplied in the original packaging of the generic manufacturer and labeled with the clinical label.

ABBV-951 and placebo solution for ABBV-951 will be supplied as solution for infusion in vials labeled in a blinded fashion and packaged in a carton containing 7 vials per carton. Each vial and carton will be labeled as required per country requirements. Each label must remain affixed to the vial and carton.

The over-encapsulated CD/LD IR tablets and placebo capsules for CD/LD IR will be supplied in bottles and labeled with the clinical label.

AbbVie will supply blinded study drug solution, blinded oral study drug, open-label CD/LD IR tablets for the Oral CD/LD Stabilization Period and as rescue therapy, the study pump and its accessories, syringe/drug reservoir, infusion sets, and vial adapters.

Storage and Disposition of Study Drug

Study drug solution must be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Study drug solution must be allowed to warm to room temperature in the sealed vial for 30 minutes prior to transfer to the drug reservoir/syringe. Oral study drug must be stored at room temperature 15°C to 25°C (59°F to 77°F) and protected from light. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug and devices supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until the time of use or until returned to AbbVie.

Tote bags, cold packs, cooler bags, and disposal containers may be provided to study subjects.

The PM-PDSC Pump Delivery System, including the infusion pump, infusion set, vial, vial adapter, and syringes, must be used as indicated and training will be provided to clinical study personnel and/or a sponsor-provided home care nurse. See Section 3.18 of the Operations Manual (Appendix F) for additional information regarding PM-PDSC Pump Delivery System training.

Detailed IFUs will be provided to clinical study personnel for programming the pump, to subjects for using the PM-PDSC Pump Delivery System to administer the solution for infusion, and to subjects for preparing study drug. Detailed IFUs will also be provided to subjects for using carrying accessories, the infusion set, the vial adapter, and the battery charging station.

The site is required to hand write the expiry date generated by the IRT system on the pump label when the pump is dispensed to a subject.

Study Drug/Study Devices Accountability

The investigator or his/her 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.

Subjects will be instructed to return all vials within the original vial carton at each visit; used drug vials will be returned with vial adapters attached. Subjects will also be instructed to return unused tablets

and capsules in the original containers at each visit. Used syringes and used 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 alternate sponsor-approved method of disposal shall be used. The subject will return any remaining unused syringes, infusion sets (inserter and infusion set tubing), and vial adapters 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 will 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) dispensed by the site. Returned study drug should not be re-dispensed to the subject.

See Section 3.19 of the Operations Manual (Appendix F) for additional information regarding dispensation and return of the PM-PDSC Pump Delivery System.

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 Randomization/Drug Assignment

Subject Identifier Assignment

An IRT system will assign a unique identification number to each subject at V1. For subjects who do not meet the study selection criteria to be enrolled in the Oral CD/LD Stabilization Period, clinical study personnel must register the subject as a screen failure in the IRT system.

Treatment of study drug solution and oral study drug will be administered in a blinded manner during the Double-Blind Treatment Period.

Subjects who are enrolled will retain the subject number assigned to them at 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

At Day 1/Randomization Visit (V6), after confirming that the subject continues to meet study selection criteria, the IRT will randomize the subject to receive one of the following double-blind treatments for 12 weeks, using a 1:1 randomization ratio:

- 24-hour/day CSCI of ABBV-951 plus oral placebo capsules for CD/LD IR

  OR

- 24-hour/day CSCI of placebo solution for ABBV-951 plus encapsulated CD/LD IR tablets.

A CSCI of ABBV-951 study drug or placebo solution will be delivered over 24 hours daily for up to 12 weeks via an infusion set connected to a pump. Each subject's starting continuous infusion rate will be calculated based on the subject's daily LD intake during the waking time at the end of the Oral CD/LD

Stabilization Period and an algorithm developed following the analysis of pharmacokinetic data from Phase 1 studies. The infusion rates might be adjusted only during the CSCI Optimization Phase.

5.10 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 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 biologic or drug component of the product or to the medical device component(s).

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

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

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.

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 which 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.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations," such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The 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 a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre 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 the CRO (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 (Appendix F) 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 Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the 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 time of study drug administration 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.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

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

Adverse Events of Special Interest

The following AESIs will be monitored during the study:

- Polyneuropathy
- Weight loss
- Somnolence
- Hallucinations/psychosis

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 reviewing and managing psychogenic concomitant medications (including those for the management of PD, especially dopamine agonist) prior to enrollment in the

study. Should hallucinations appear during the study, standard of care may be applied. This should include a conservative approach of assessing alternate etiologies and addressing them as appropriate and if none are found, waiting a few days to see if the phenomenon resolves spontaneously. However, the ultimate decision on how an individual subject is managed during the study is the decision 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 blinded review of moderate and severe infusion site–related reactions will be performed.

Adverse Event Severity and Relationship to Study Drug

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

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

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE 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 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 an SAE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - circumstances had been less fortunate will be reported.
- 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 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 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 partners 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

The statistical methods provided in this protocol are focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described and fully documented in the SAP.

The final analyses will be conducted following database lock after all subjects have completed V13 (Week 12) or prematurely discontinued. Study sites and subjects will remain blinded to the treatment assignment during the Double-Blind Treatment Period for the duration of the study.

Baseline for PD Diary variables will be the average of the 3 valid diaries completed before Day –1. Baseline for all efficacy and safety measures, other than the PD Diary, will be defined as the last nonmissing observation that is before the day of randomization, with the exception of vital sign

variables which will be the average of observations if multiple measurements are obtained on the same day.

Postbaseline efficacy and safety measures, other than AE and infusion site evaluation, collected more than 1 day after the last dose of double-blind study drug will not be used for efficacy and safety analyses because data after discontinuation of study drug may be confounded by the various PD treatments that the subject may be on after discontinuing study treatment.

7.2 Definition for Analysis Populations

The Oral CD/LD Analysis Set includes all subjects who received at least 1 dose of open-label CD/LD IR tablets during the Oral CD/LD Stabilization Period. The Oral CD/LD Analysis Set will be used to summarize premature discontinuations and AEs during the Oral CD/LD Stabilization Period.

The Full Analysis Set (FAS) includes all randomized subjects who received any dose of study drug during the Double-Blind Treatment Period and who have baseline and at least 1 postbaseline observation for at least 1 efficacy assessment. The subject will be grouped according to treatment as randomized. The FAS will be used for all efficacy and baseline analyses for the Double-Blind Treatment Period.

The Safety Analysis Set consists of all subjects who received any dose of study drug during the Double-Blind Treatment Period. Subjects will be grouped according to treatment received regardless of randomization. The safety analysis set will be used for all safety analyses for the Double-Blind Treatment Period.

7.3 Statistical Analyses for Efficacy

Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Week 12 of the Double-Blind Treatment Period in average daily normalized "On" time without troublesome dyskinesia (hours). The normalized "On" time without troublesome dyskinesia is the sum of the normalized "On" time without dyskinesia and the normalized "On" time with non-troublesome dyskinesia. A valid diary day is defined as one that does not have more than 2 hours of missing data (4 or less missing 30-minute entries) for the entire 24-hour diary. The sum of absolute "On" times without dyskinesia and "On" times with non-troublesome dyskinesia collected on each valid PD Diary day will be normalized to a typical waking day (16 hours) to account for different sleep patterns across subjects:

> Normalized "On" time without troublesome dyskinesia = (Absolute "On" time without troublesome dyskinesia/Awake time) × 16

and averaged over 3 consecutive diary days to obtain the average daily normalized "On" time without troublesome dyskinesia for each visit.

The primary analysis will utilize a mixed model for repeated measures (MMRM) and include data on change from baseline to each post-baseline visit in average daily normalized "On" time without troublesome dyskinesia obtained from PD diaries. The model will include fixed categorical effects of treatment, country and visit, baseline-by-visit and treatment-by-visit interactions, and baseline as a

covariate. An unstructured variance-covariance matrix will be used. In this analysis, missing data in subjects who prematurely discontinue during the Double-Blind Treatment Period will be handled in the MMRM model based on the missing at random assumption, and model parameters will be estimated using the restricted maximum likelihood method. The primary comparison will be the contrast between the ABBV-951 + placebo capsules and placebo solution + CD/LD IR treatment arms at Week 12 of the Double-Blind Treatment Period.

Secondary Efficacy Analysis

The following key secondary and other secondary endpoints will be included in multiplicity adjustment of the Type I error to control the familywise error rate (FWER) at 2-side significance level of 0.05 for the entire study.

- Key secondary endpoints:
  - Change from Baseline to Week 12 of the Double-Blind Treatment Period in hours of average daily normalized "Off" time as assessed by the PD Diary
  - Change from Baseline to Week 12 of the Double-Blind Treatment Period in MDS-UPDRS Part II score
  - Presence of morning akinesia at Week 12 as assessed by the PD Diary
- Other secondary endpoints that are included in the FWER control:
  - Change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia as assessed by the PD Diary
  - Change from Baseline to Final Visit in PDSS-2 total score
  - Change from Baseline to Final Visit in PDQ-39 summary index
  - Change from Baseline to Final Visit in EQ-5D-5L summary index
  - Change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the PKG wearable device
  - Change from Baseline to Week 12 in interquartile range of bradykinesia score (BK75-BK25) as assessed by the PKG wearable device
  - Change from Baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device
  - Change from Baseline to Week 12 in interquartile range of dyskinesia score (DK75-DK25) as assessed by the PKG wearable device

Change from Baseline to Week 12 in average normalized "Off" time, MDS-UPDRS Part II score, average normalized "On" time without dyskinesia, and PKG variables will be analyzed using the same MMRM model as the primary efficacy analysis.

Change from Baseline to Final Visit in PDSS-2 total score, PDQ-39 summary index, and EQ-5D-5L summary index will be analyzed using an analysis of covariance model with the categorical fixed effects of treatment and country, and baseline score as a covariate.

The first morning status upon awakening at each postbaseline visit will be analyzed using a generalized linear mixed model with a logit link function to compare the probability of having morning akinesia between the treatment groups. The model will include fixed categorical effects of treatment, country and visit, treatment-by-visit interaction, and baseline first morning status upon awakening. An unstructured variance-covariance matrix will be used. The primary comparison for this analysis will be the odds ratio between the ABBV-951 + placebo capsules and placebo solution + CD/LD IR groups at Week 12.

Sensitivity Analysis of the Primary Efficacy Analysis

A sensitivity analysis on handling missing data due to premature discontinuation will be conducted on the primary efficacy endpoint of change from Baseline to Week 12 in average daily normalized "On" time without troublesome dyskinesia. This analysis will employ the "jump-to-reference" analytic approach to account for missing data in subjects who prematurely discontinue during the Double-Blind Treatment Period. Details for the implementation of this approach will be described in the SAP.

Additional Efficacy Analyses

Details on other efficacy analyses will be provided in the SAP.

Subgroup Analysis for Efficacy

Subgroup analyses of the primary endpoint of change from Baseline to Week 12 of the Double-Blind Treatment Period in average normalized "On" time without troublesome dyskinesia will be conducted for the following subgroups:

- Age category (< 65 years or ≥ 65 years)
- Sex (male or female)
- Race (white or other)
- Country
- Duration of PD since diagnosis (< 10 years or ≥ 10 years)
- Concomitant dopamine agonist use (yes or no)
- Dose category (low or high levodopa dose). Details on how to define the dose category will be described in the SAP.

A subgroup analysis may not be conducted if one category of the subgroup variable comprises < 20% of the FAS Analysis Set.

7.4 Statistical Analyses for Safety

General Considerations

Adverse events during the Oral CD/LD Stabilization Period will be analyzed using the Oral CD/LD Analysis Set. Safety analyses for the Double-Blind Treatment Period will be carried out using the Safety Analysis Set. Safety will be assessed by AEs, laboratory values, vital sign measurements, ECG, C-SSRS and QUIP-RS. For continuous safety outcomes, the change from Baseline will be analyzed in a descriptive

manner by treatment group and by visit. For categorical safety outcomes, the number and percentage of each category will be summarized by treatment group and by visit. Shift of laboratory values from Baseline to defined time points will be tabulated. Hypothesis testing will not be performed for safety parameters.

Analysis of Adverse Events

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, treatment-emergent SAEs, AESIs, AEs with a reasonable possibility of being related to study drug, AEs leading to study drug discontinuation during the Double-Blind Treatment Period will be summarized by treatment group and will be tabulated using primary MedDRA system organ class and preferred term. Treatment emergent AEs for the Oral CD/LD Stabilization Period will be defined as all events that begin or worsen on or after first dose of open-label CD/LD IR tables during the Oral CD/LD Stabilization Period and prior to first dose of blinded study drug during the Double-Blind Treatment Period. Treatment emergent AEs for the Double-Blind Treatment Period will be defined as all events that begin or worsen on or after first dose of study drug during the Double-Blind Treatment Period. AEs with onset on the first day of blinded study drug will be considered treatment-emergent for the Double-Blind Treatment Period.

Analysis of Laboratory Data

Changes from Baseline to the final value during the Double-Blind Treatment Period in continuous laboratory parameters will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group and all subjects overall for each continuous hematology, chemistry, and urinalysis variable.

Changes in laboratory parameters from Baseline to the final value will be tabulated using shift tables either by Common Terminology Criteria for Adverse Events (CTCAE) grades or categorized as low, normal, or high based on the normal ranges of the laboratory that performed the assay.

For each hematology, chemistry and urinalysis variable that potentially clinically significant (PCS) criteria are defined, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criterion and is more extreme than their baseline value will be provided for each treatment group and all subjects overall.

Analysis of Vital Signs

Change from Baseline to each planned visit and to the minimum, maximum and final value during the Double-Blind Treatment Period will be summarized in a descriptive manner for each treatment group and all subjects overall for each vital sign and weight variable. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided for each treatment group and all subjects overall.

Other Safety Analysis

Further details and additional safety analyses will be specified in the SAP.

7.5 Interim Analysis

No interim analysis on efficacy or safety data is planned for this study.

7.6 Multiplicity Adjustment and Overall Type I Error Control

In order to control the familywise error rate at 2-side significance level of 0.05 for the entire study, a fixed sequence testing procedure will be used for the primary, key secondary and other secondary endpoints. Only if success has been demonstrated for the primary endpoint of change from Baseline to Week 12 in average daily normalized "On" time without troublesome dyskinesia, will the testing proceed to the key secondary and other secondary endpoints in the following order:

- Change from Baseline to Week 12 in hours of average daily normalized "Off" time
- Change from Baseline to Week 12 in MDS-UPDRS Part II score
- Presence of morning akinesia at Week 12
- Change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia
- Change from Baseline to Final Visit in PDSS-2 total score
- Change from Baseline to Final Visit in PDQ-39 summary index
- Change from Baseline to Final Visit in EQ-5D-5L summary index
- Change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the PKG wearable device
- Change from Baseline to Week 12 in interquartile range of bradykinesia score (BK75-BK25) as assessed by the PKG wearable device
- Change from Baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device
- Change from Baseline to Week 12 in interquartile range of dyskinesia score (DK75-DK25) as assessed by the PKG wearable device

7.7 Sample Size Determination

Assuming that the difference in change from Baseline to Week 12 in average daily normalized "On" time without troublesome dyskinesia is 1.86 hours between ABBV-951 + placebo capsules and placebo solution + CD/LD IR treatment arms, and the common standard deviation is 2.9 hours, a sample size of 52 subjects per arm will have a 90% power to detect a statistically significant difference between the 2 treatment arms with a 2-sided significance level of 0.05. Approximately 130 subjects will be randomized assuming that approximately 20% of subjects will prematurely discontinue during the Double-Blind Treatment Period. This sample size also has approximately 90% power for key secondary endpoints of change from Baseline in normalized "Off" time, MDS-UPDRS Part II score, and presence of morning akinesia.

An adequate number of subjects will be enrolled in the Oral CD/LD Stabilization Period to meet the randomization goal of the study.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

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.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual (Appendix F), 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 of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in an effort 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 lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to the Operations Manual in Appendix F for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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

1. AbbVie. ABBV-951 Investigator's Brochure.

2. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649-53.

3. Espay AJ, Pagan FL, Walter BL, et al. Optimizing extended-release carbidopa/levodopa in Parkinson disease: Consensus on conversion from standard therapy. Neurol Clin Pract. 2017;7(1):86-93.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
25/100	25 mg/100 mg
AE	adverse event
AESI	adverse event of special interest
aPD	advanced Parkinson's Disease
CD	carbidopa
CD/LD	carbidopa/levodopa
CDP/LDP	carbidopa phosphate/levodopa phosphate
CDP	carbidopa phosphate
CLES	carbidopa-levodopa enteral suspension
COMT	catechol-*O*-methyltransferase
COVID-19	coronavirus disease - 2019
CSCI	continuous subcutaneous infusion
C-SSRS	Columbia-Suicide Severity Rating Scale
DO	Doctor of Osteopathic Medicine
DTP	direct-to-patient
ECG	electrocardiogram
eCRF	electronic case report form
FAS	Full Analysis Set
FWER	familywise error rate
GCP	Good Clinical Practice
ICD	impulse control disorder
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFU	instructions for use
IMP	investigational medicinal product
IR	immediate release
IRB	institutional review board
IRT	interactive response technology

ISE	Infusion Site Evaluation
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
LCIG	levodopa-carbidopa intestinal gel
LD	levodopa
LDP	levodopa phosphate
MAO	monoamine oxidase
MD	Doctor of Medicine
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
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
nM-EDL	Non-Motor Aspects of Experiences of Daily Living
NP	Nurse Practitioner
OUS	outside the United States
PA	Physician's Assistant
PCS	potentially clinically significant
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39 item
PDSS-2	Parkinson's Disease Sleep Scale-2
PhD	Doctor of Philosophy
PKG	Parkinson's KinetiGraph® or Personal KinetiGraph® (United States)
PM-PDSC	Phillips-Medisize - Parkinson's Disease Subcutaneous
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
RLS	restless leg syndrome
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan

SSR	sample size re-estimation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	therapeutic area medical director
US	United States
VAS	visual analogue scale

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M15-736: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients

Protocol Date: 10 September 2021

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 operations manual, 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]	[redacted]	Neuroscience Development
		Neuroscience Development
		Data and Statistical Sciences
		Neuroscience Development
		Clinical Program Development
		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). Allowed modifications due to COVID-19 are detailed within the Operations Manual. Subjects who prematurely discontinue before the Randomization Visit (V6) do not need to complete V13 assessments; a follow-up visit or phone call will be completed 30 days after the last dose of study drug, if the subject is willing, to ensure all treatment-emergent AEs/SAEs have been resolved. If a subject prematurely discontinues blinded study drug, V13 assessments (also the Premature Discontinuation Visit for the Double-Blind Treatment Period) should be completed as soon as possible, preferably within 2 weeks.

Study Activities Table

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
INTERVIEWS & QUESTIONNAIRE														
Subject information and informed consent (caregiver to also provide consent, if applicable)	✓													
Eligibility criteria *investigator or designee to confirm eligibility in EDC (sponsor available to discuss any questions regarding appropriateness of study participation for a specific subject or the eligibility criteria)	✓	✓*	✓	✓	✓	✓ (Predose)								

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
PM-PDSC Knowledge and Skills Checklist (*may be repeated at an unscheduled visit prior V3)		✓*			✓									
Medical/surgical history	✓ Base-line													
Alcohol and nicotine use	✓													
Clinical Assessment	✓													
Infusion site evaluation (dermatologic assessment if applicable)							✓	✓	✓	✓	✓	✓	✓	✓
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Product complaints	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
Exit Interview (to be conducted after all other study procedures)													✓	
Patient Reported Outcomes: Patient Administered Measures (specific time points)														
Subject Dosing Diary (for 3 consecutive days before each visit)								✓	✓	✓	✓	✓	✓	
Subject Dosing Diary to record all oral CD/LD IR rescue						✓	✓	✓	✓	✓	✓	✓	✓	
Infusion Site Rotation Tool (every time infusion site is changed)						✓	✓	✓	✓	✓	✓	✓	✓	
Parkinson's Disease Diary Concordance	✓													

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
Parkinson's Disease Diary (for 3 consecutive days before each visit). *44 of 48 entries required each 24-hour period **must be started at least 4 days prior to Day 1, i.e., PD Diary needs to be completed prior to Day –1)		✓*				✓*, ** Baseline		✓	✓	✓	✓	✓	✓	
EQ-5D-5L					✓								✓	
PKG watch (wearable device)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Patient Reported Outcomes: Site Rater Administered Measures (specific time points)														
MMSE	✓													
MDS-UPDRS	✓				✓		✓	✓	✓	✓	✓	✓	✓	
C-SSRS *Baseline	✓*	✓			✓	✓ (predose)	✓	✓	✓	✓	✓	✓	✓	
QUIP-RS	✓				✓				✓		✓		✓	

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
Patient Reported Outcomes: Central Rater Administered Measures (specific time points)														
PDSS-2	✓				✓								✓	
PDQ-39	✓				✓								✓	
Exams & Labs														
Height (V1 only)/ weight	✓	✓	✓	✓	✓	✓ (predose)	✓	✓	✓	✓	✓	✓	✓	
Orthostatic vital signs	✓	✓	✓	✓	✓ (3 sets)	✓ (pre- and post-dose)	✓	✓	✓	✓	✓	✓	✓	
Physical examination *Baseline	✓*				✓				✓		✓		✓	
Neurological examination	✓				✓								✓	
12-lead ECG	✓				✓	✓			✓		✓		✓	
Clinical laboratory tests	✓				✓								✓	

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
Special laboratory tests (vitamins B_6 and B_{12}, folic acid, MMA, homocysteine)	✓				✓								✓	
Drug screen	✓													
Serum pregnancy test	✓													
Urine pregnancy test			✓			✓ (predose)					✓	✓	✓	
℞ TREATMENT														
Dispense, verify supply of, and reconcile CD/LD IR tablets for oral stabilization			✓	✓	✓	✓								
Study drug prescription record			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
Initial subject and caregiver (if applicable) PM-PDSC Pump Delivery system training	✓				✓									
Continued PM-PDSC Pump Delivery system training		As needed												
Randomization/ study drug assignment						✓								
Dispense/return of study drug, PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy						✓	✓	✓	✓	✓	✓	✓	✓	
Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries						✓	✓	✓	✓	✓	✓	✓		

Activity	Screening Period 6 – 60 Days		Oral CD/LD Stabilization Period 14 – 21 Days			Double-Blind Treatment Period (12 Weeks)								Post-Treatment For Premature Discontinuations and completers who do not enter extension study
			Stabilization		No Change	CSCI Optimization Phase						Maintenance Phase		
	V1	V2	V3	Optional V4	V5 Baseline (unless otherwise indicated)	V6 Randomization	V7	V8	V9	Optional V10	V11	V12	V13/Premature Discontinuation	
	(6 days minimum)		(7 days minimum)		(7 days)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Post 30 Days
Reconcile study drug and PM-PDSC Pump Delivery System						✓	✓	✓	✓	✓	✓	✓	✓	

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	22 October 2019
Version 2.0	23 January 2020
Version 3.0	26 March 2020
Version 4.0	04 September 2020

The purpose of this version is to make minor clerical edits and corrections for clarity and consistency throughout the protocol, as well as to change the list and ranking of secondary endpoints included in Type I error control prior to database lock and unblinding of Study M15-736. The changes to secondary endpoints are based on results from an interim analysis of open-label Phase 3 Study M15-741 as follows:

- Moved presence of morning akinesia at Week 12 from other secondary endpoints to key secondary endpoints.
- Added change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia to the list of other secondary endpoints.
- Moved PDSS-2 total score up in the list of other secondary endpoints so that it is ranked before the PDQ-39 summary index and EQ-5D-5L summary index.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M15-736

Advanced Parkinson's Disease: Double-Blind, Double-Dummy, Active-Controlled, Efficacy and Safety Study of ABBV-951 Versus Oral Carbidopa/Levodopa

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-951

FULL TITLE: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients

1 CONTACTS

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual 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 updates below on how to proceed.

If a subject has screened, and is unable to complete screening activities on site after Screening Visit 1, it is preferable to extend the Screening Period as described below in Section 2.1 rather than perform remote Visits 3 and 4 (optional), because Visit 5 must be performed on site. The guidance that is provided for Visit 3 and beyond should be followed if the COVID-19 restrictions at your site have changed once your subject is enrolled, or after they have been randomized.

This guidance leverages the home health nurses (HHN) that are provided for the study. Sites unable to use this service due to institutional or IRB policy, or another reason approved by AbbVie should contact their primary site monitor.

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, Visits 2, 3, 4, and 7, 8, 9, 10, 11, and 12 may be conducted in the subject's home residence.
- Some study visits and/or activities may be performed by phone/virtually. These are indicated by a hashtag (**#**) in the appropriate visit tables below.
- Some study visits and/or activities may be performed in person at the subject's home by an HHN, the site staff or direct-to-patient delivery, depending on the activity. These are indicated by an asterisk (*****) in the appropriate visit tables below.
- Some study visits and/or activities may be performed by phone/virtually in conjunction with a person at the subject's home: health nurse, the site staff or direct-to-patient delivery, depending on the activity. These are indicated by an asterisk and hashtag (***#**) in the appropriate visit tables below.
- During a virtual 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 COVD-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 Visit 5, Visit 6, and Visit 13, if the visit cannot be rescheduled within the visit window, contact the sponsor. Subjects should remain on the prescribed oral CD/LD IR regimen and

concomitant PD medication until starting blinded study drug at V6, and remain on the double-blind study drug as much as possible through D85/Premature Discontinuation Visit (V13) even if a visit is not occurring on the designated study day.

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

2.1 Screening Period Activities

This section presents a list of activities performed at Screening Visit 1 (V1) and Screening Visit 2 (V2). 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 (caregiver to also provide consent, if applicable) • Evaluate eligibility criteria • Medical/surgical history (Baseline) • Alcohol and nicotine use • Clinical assessment	• Adverse event (AE) assessment • Product complaints • Prior/concomitant therapy assessment
PATIENT REPORTED OUTCOME (PRO)	• Parkinson's disease (PD) diary concordance[a] • Provide Parkinson's KinetiGraph®/Personal KinetiGraph® (PKG) (to age eligible subjects in countries where allowed) • Columbia-Suicide Severity Rating Scale (C-SSRS) (Baseline) • Questionnaire for Impulsive-Compulsive Disorders in PD-Rating (QUIP-RS)	• Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS) • Mini-Mental State Examination (MMSE) • Parkinson's Disease Questionnaire-39 item (PDQ-39) (central rater administered) • Parkinson's Disease Sleep Scale-2 (PDSS-2) (central rater administered)
EXAM	• Height and weight • Orthostatic vital signs	• Physical (Baseline)/neurological exam • 12-lead electrocardiogram (ECG)
LAB	• Clinical laboratory tests (central lab) • Special laboratory tests (central lab)	• Drug screen • Serum pregnancy test (central lab)
TREATMENT	• Initial Phillips-Medisize - Parkinson's Disease Subcutaneous (PM-PDSC) Pump Delivery System training[b]	

a. Subjects who fail to meet this requirement may repeat the PD Diary for 3 additional consecutive days prior to V3. If the "Off" time criterion is still not met, subjects must be screen failed.

b. PM-PDSC Pump Delivery System training will be initiated during V1 and can be continued as needed throughout the study.

NOTES: V1 may be split into different visits.
All Screening Visit 1 procedures must be performed onsite.

SCREENING Visit 2 (V2):

INTERVIEW	# Evaluate eligibility criteria (confirm eligibility in EDC; sponsor available to discuss any questions regarding appropriateness of a specific subject criteria) # Adverse event (AE) assessment # Product complaints	# Prior/concomitant therapy assessment * PM-PDSC Knowledge and Skills Checklist[a]
PRO	• PD Diary (3 consecutive days before visit; site phone call reminder 4 days prior) • Wear PKG (in countries where allowed)	# C-SSRS (Since Last Visit)
EXAM	• Weight – Orthostatic vital signs	
TREATMENT	* PM-PDSC Pump Delivery System training (as needed)	

a. Subject (or caregiver, if applicable), must demonstrate understanding and correct use of the PM-PDSC Pump Delivery System, including inserting the cannula into the subject's abdomen, as assessed by the investigator or designee.

2.2 Oral CD/LD Stabilization Period Activities

This section presents a list of activities performed during each visit in the Oral CD/LD Stabilization Period, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall period.

Activities are grouped by category (Interview, Exam, etc.). Details about each activity are provided in Section 3.

Visit 3 (V3):

INTERVIEW	#	Evaluate eligibility criteria	#	Prior/concomitant therapy assessment
	#	AE assessment		
	#	Product complaints		
PRO	•	Wear PKG (in countries where allowed)		
EXAM	–	Weight	–	Orthostatic vital signs
LAB	*#	Urine pregnancy test		
TREATMENT	*#	Study drug prescription record	*	Dispense, verify supply of, and reconcile CD/LD IR tablets for oral stabilization
	*	PM-PDSC Pump Delivery System training (as needed)		

Visit 4 (V4) (optional):

INTERVIEW	#	Evaluate eligibility criteria	#	Prior/concomitant therapy assessment
	#	AE assessment		
	#	Product complaints		
PRO	•	Wear PKG (in countries where allowed)		
EXAM	–	Weight	–	Orthostatic vital signs
TREATMENT	*#	Study drug prescription record	*	Dispense, verify supply of, and reconcile CD/LD IR tablets for oral stabilization
	*	PM-PDSC Pump Delivery System training (as needed)		

Baseline[a] Visit 5 (V5):

INTERVIEW	• Evaluate eligibility criteria • AE assessment • Product complaints	• Prior/concomitant therapy assessment • PM-PDSC Knowledge and Skills Checklist[b]
PRO	• EQ-5D-5L • Wear PKG (in countries where allowed) • MDS-UPDRS	• C-SSRS • QUIP-RS • PDSS-2 (central rater administered) • PDQ-39 (central rater administered)
EXAM	• Weight • Orthostatic vital signs (3 sets)	• Physical/neurological exam • 12-lead ECG
LAB	• Clinical laboratory tests (central lab) • Special laboratory tests (central lab)	
TREATMENT	• Study drug prescription record • PM-PDSC Pump Delivery System training (as needed)	• Dispense, verify supply of, and reconcile CD/LD IR tablets for oral stabilization

a. Unless otherwise indicated.

b. Subject (or caregiver, if applicable) must demonstrate understanding and correct use of the PM-PDSC Pump Delivery System, including inserting the cannula into the subject's abdomen, as assessed by the investigator or designee.

NOTE: All Visit 5 procedures must be performed onsite.

2.3 Double-Blind Treatment Period Activities

A list of activities performed during each visit in the double-blind Treatment Period, 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.

Randomization Visit 6 (V6) (Day 1):

INTERVIEW	• Evaluate eligibility criteria[a] • AE assessment[b] • Product complaints	• Prior/concomitant therapy assessment
PRO	• PD Diary (3 consecutive days before visit; must be completed prior to Day –1; site phone call reminder) (Baseline)	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[c] • C-SSRS
EXAM	• Weight[a] • Orthostatic vital signs[a,b]	• 12-lead ECG[b]
LAB	• Urine pregnancy test[a]	
TREATMENT	• Study drug prescription record • PM-PDSC Pump Delivery System training (as needed) • Randomization • Dispense study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	• Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries • Return/reconcile CD/LD IR tablets used for oral stabilization

a. Before blinded study drug initiation (pre-dose).

b. After blinded study drug initiation (post-dose).

c. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

NOTES: If not needed, activities should be completed post-dose to minimize subject's time in the "Off" state.

All Visit 6 procedures must be performed onsite.

Visit 7 (V7) (Day 2):

INTERVIEW	# Infusion site evaluation (dermatologic assessment if applicable) # AE assessment # Product complaints	# Prior/concomitant therapy assessment
PRO	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[a]	# MDS-UPDRS # C-SSRS
EXAM	– Weight	– Orthostatic vital signs
TREATMENT	* Study drug prescription record * PM-PDSC Pump Delivery System training (as needed) * Dispense/return of study drug and PM-PDSC Pump Delivery System	* Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries * Reconcile study drug and PM-PDSC Pump Delivery System

a. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

Visit 8 (V8) (Day 8):

INTERVIEW	# Infusion site evaluation (dermatologic assessment if applicable) # AE assessment # Product complaints	# Prior/concomitant therapy assessment
PRO	• Subject Dosing Diary (3 consecutive days before visit; site phone call reminder) • PD Diary (3 consecutive days before visit; site phone call reminder)	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[a] # MDS-UPDRS # C-SSRS
EXAM	– Weight	– Orthostatic vital signs
TREATMENT	*# Study drug prescription record * PM-PDSC Pump Delivery System training (as needed) * Dispense/return of study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	* Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries * Reconcile study drug and PM-PDSC Pump Delivery System

a. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

Visit 9 (V9) (Day 15):

INTERVIEW	# Infusion site evaluation (dermatologic assessment if applicable) # AE assessment # Product complaints	# Prior/concomitant therapy assessment
PRO	• Subject Dosing Diary (3 consecutive days before visit; site phone call reminder) • PD Diary (3 consecutive days before visit; site phone call reminder)	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[a] # MDS-UPDRS # C-SSRS # QUIP-RS
EXAM	– Weight – Orthostatic vital signs	– Physical exam – 12-lead ECG
TREATMENT	*# Study drug prescription record * PM-PDSC Pump Delivery System training (as needed) * Dispense/return of study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	* Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries * Reconcile study drug and PM-PDSC Pump Delivery System

a. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

Visit 10 (V10) (Day 22) (optional[a]):

INTERVIEW	# Infusion site evaluation (dermatologic assessment if applicable) # AE assessment # Product complaints	# Prior/concomitant therapy assessment
PRO	• Subject Dosing Diary (3 consecutive days before visit; site phone call reminder) • PD Diary (3 consecutive days before visit; site phone call reminder)	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[b] # MDS-UPDRS # C-SSRS
EXAM	– Weight	– Orthostatic vital signs
TREATMENT	*# Study drug prescription record * PM-PDSC Pump Delivery System training (as needed) * Dispense/return of study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	* Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries * Reconcile study drug and PM-PDSC Pump Delivery System

a. Phone contact will be needed prior to the visit to review the Subject Dosing Diary and Parkinson's Disease Diary entries and determine if this visit is needed.

b. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

Visit 11 (V11) (Day 29):

INTERVIEW	# Infusion site evaluation (dermatologic assessment if applicable) # AE assessment # Product complaints	# Prior/concomitant therapy assessment
PRO	• Subject Dosing Diary (3 consecutive days before visit; site phone call reminder) • PD Diary (3 consecutive days before visit; site phone call reminder)	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[a] # MDS-UPDRS # C-SSRS # QUIP-RS
EXAM	– Weight – Orthostatic vital signs	– Physical exam – 12-lead ECG
LAB	*# Urine pregnancy test	
TREATMENT	*# Study drug prescription record * PM-PDSC Pump Delivery System training (as needed) * Dispense/return of study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	* Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries * Reconcile study drug and PM-PDSC Pump Delivery System

a. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

Visit 12 (V12) (Day 57):

INTERVIEW	# Infusion site evaluation (dermatologic assessment if applicable) # AE assessment # Product complaints	# Prior/concomitant therapy assessment
PRO	• Subject Dosing Diary (3 consecutive days before visit; site phone call reminder) • PD Diary (3 consecutive days before visit; site phone call reminder)	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[a] # MDS-UPDRS # C-SSRS
EXAM	– Weight	– Orthostatic vital signs
LAB	*# Urine pregnancy test	
TREATMENT	*# Study drug prescription record * PM-PDSC Pump Delivery System training (as needed) * Dispense/return of study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	* Verify supply of study drug, PM-PDSC Pump Delivery System, and ancillaries * Reconcile study drug and PM-PDSC Pump Delivery System

a. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

Visit 13 (V13) (Day 85) or Premature Discontinuation from Double-Blind Treatment Period:

INTERVIEW	• Infusion site evaluation (dermatologic assessment if applicable) • AE assessment • Product complaints	• Prior/concomitant therapy assessment • Exit Interview (to be conducted after all other study procedures)
PRO	• Subject Dosing Diary (3 consecutive days before visit; site phone call reminder) • PD Diary (3 consecutive days before visit; site phone call reminder) • EQ-5D-5L	• Wear PKG (in countries where allowed) • Infusion Site Rotation Tool[a] • MDS-UPDRS • C-SSRS • QUIP-RS • PDSS-2 (Central Rater administered) • PDQ-39 (Central Rater administered)
EXAM	• Weight • Orthostatic vital signs	• Physical/neurological exam • 12-lead ECG
LAB	• Clinical laboratory tests (central lab)	• Special laboratory tests (central lab) • Urine pregnancy test
TREATMENT	• Study drug prescription record • PM-PDSC Pump Delivery System training (as needed) • Return of study drug and PM-PDSC Pump Delivery System, and CD/LD IR tablets for rescue therapy	• Reconcile study drug and PM-PDSC Pump Delivery System

a. Recorded every time the infusion site is changed during the Double-Blind Treatment Period.

NOTE: Visit 13 procedures must be performed onsite.

2.4 Post-Treatment Activities

There are no post-treatment activities except for subjects who prematurely discontinue study participation. See Protocol Section 5.7 for additional information.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject (and caregiver, if applicable) and 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(s) 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. If a caregiver will be trained on the PM-PDSC Pump and/or will be participating in the Exit Interview, the caregiver will also be required to provide consent.

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

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol 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.

Informed consent will be obtained at Screening Visit 1 (V1) as shown in Section 2.1.

3.2 Eligibility Criteria

All subjects will be evaluated to ensure they meet the eligibility criteria during the Screening Period. Subjects must meet all eligibility criteria prior to the Oral CD/LD Stabilization Period and the administration of open-label oral study drug at V3. Subjects must continue to meet these eligibility criteria prior to randomization (V6) and administration of double-blind study drug.

Note: At V2 and prior to a subject's enrollment (V3), the investigator or designee must confirm eligibility criteria in EDC. The TA MD or designee [contact information on cover page] are readily available to discuss any questions the Investigator or designee may have regarding appropriateness of study participation for a specific subject or the eligibility criteria. The decision to enroll the subject is ultimately the investigator's responsibility.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If the Screening Period cannot be completed within 60 days due to an extenuating event (e.g., genuine emergency, natural disaster), contact the TAMD for a case-by-case review and approval of potential rescreens (e.g., due to COVID-19-related disruptions) that prevent screening within 60 days.

Rescreened subjects will need to repeat all screening visits and screening procedures (except for the concordance testing) and demonstrate that they still qualify prior to enrollment (V3).

3.3 PM-PDSC Pump Delivery System Training (Screening Through Enrollment)

Leading up to V2, subjects (and caregivers, if applicable) will continue to be trained on the correct use of the PM-PDSC Pump Delivery System at the study site or the subject's home. At V2, the subject (or caregiver) must demonstrate the understanding and correct use of the delivery system, including the insertion of the cannula into the subject's abdomen, as assessed by the investigator or designee using the PM-PDSC Knowledge and Skills Checklist. Subjects who fail this requirement may repeat it once (at an unscheduled visit prior to V3) but must be screen failed if the criterion is still not met. Additionally, during the Screening Period, subjects may become familiar with and simulate the experience of wearing a delivery system via a mock infusion delivery system where available. The mock system will approximate the dimensions, weight, tubing and other general physical features of the PM-PDSC Delivery System, but it will not be functional and subjects will not insert a cannula in their abdomen nor infuse any solution.

Subjects (and caregivers, if applicable) will continue to be trained on the correct use of the PM-PDSC Pump Delivery System leading up to V5 and must again demonstrate at V5 the understanding and correct use of the delivery system, including the insertion of the cannula into the subject's abdomen, as assessed by the investigator or designee using the PM-PDSC Knowledge and Skills Checklist. Subjects who fail this requirement must be prematurely discontinued. V5 will be the Baseline Visit, unless otherwise indicated.

3.4 Medical/Surgical History

A complete medical and surgical history, including demographics, nicotine use, and histories of alcohol or drug abuse, that in the investigator's judgment might impact compliance with study execution, will be taken at the Screening Visit 1 (V1), as shown in Section 2.1. Additionally, chronic disorders (e.g., diabetes, hypertension, hay fever, polyneuropathy) diagnosed prior to V1 and still present at V1 should be recorded on the Medical History Form. The medical history obtained at V1 will serve as the Baseline for clinical assessment. All psychiatric, neurological, 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 blinded 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.

3.5 Clinical Assessments

A clinical assessment will be conducted on all subjects at V1, as shown in Section 2.1. This will include an assessment of the subject's PD treatment history. 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 and/or caregiver's (if applicable) recollection, as well as available history in a subject's chart.

3.6 Adverse Event Assessment

Adverse events 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 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. Adverse events, 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 4.2.

3.7 Infusion Site Evaluation

The investigator or qualified designee will evaluate the infusion site area (abdomen) from Day 2 (V7) through the end of the study, at each study visit, as shown in Section 2.3. A 2-part (numeric and letter grading) evaluation scale will be used to assess irritation:[1]

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 Assessments

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 the photographs. In rare situations where an assessment or visit cannot be completed onsite due to an extenuating event (e.g., genuine emergency, natural disaster, 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 after 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, subject visits may be conducted via phone or video conference. The Infusion Site Evaluation (ISE) is eligible for completion by interview at V7, V8, V9, V10, V11, and V12. In this situation, the ISE: may be completed via video if the picture is of sufficient quality; report AEs per protocol, request subject/caregiver to describe the reaction (redness, swelling, etc.); if ISE meets criteria for dermatologic assessment, request that a photo of the reaction be provided to the site.

3.8 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.

3.9 Patient-Reported Outcomes

Patient-reported outcomes (PRO) instruments include the following:

- Self-Administered PRO Instruments: Subjects will complete the PD Diary Concordance, Subject Dosing Diary, PD Diary, and EQ-5D-5L. 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 make every effort to ensure that a response is entered for all items. Subjects will also wear the PKG watch (based on local country regulations).

- Rater-Administered PRO Instruments: Subjects will complete the following rater-administered instruments: Mini-Mental State Examination (MMSE), Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Columbia-Suicide Severity Rating Scale (C-SSRS), and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS).
    - Central Rater Required: The Parkinson's Disease Sleep Scale-2 (PDSS-2) and Parkinson's Disease Questionnaire-39 item (PDQ-39) will be administered by a qualified blinded central rater.

  All applicable clinical, safety, and health-outcome assessments will be administered only by individuals qualified by the sponsor.

  Note: 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 to minimize sources of variability.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. PROs eligible for completion by interview at such visits are V2, V3, V4, and V7, V8, V9, V10, V11, and V12. 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 videoconference 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 who collected the information.

- SLATE Device PRO (i.e., rater tablet): Preferred method is to collect data using direct entry into the SLATE device, even when collected remotely. Paper PROs can be utilized as a backup plan. Specifications are outlined below.
- Site Rater administered scales: This includes C-SSRS, MDS-UPDRS, and QUIP-RS, as applicable for each visit. The qualified rater at your site will conduct those assessments remotely except for the 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 which, in this case, should be completed with all zeros (0's) before launching a data clarification form in TrialMax to get this documented.
    - Paper PROs can be used as a backup plan.
    - **The PRO scales or screenshots have been provided to IRB/EC according to local regulations, and your site should use the version provided to the IRB/EC for paper collection in your local language. If your site is not able to pull up IRB/EC portal to obtain scale, contact your primary monitor for assistance.**

- Your source documentation should clearly indicate how each scale was obtained (e.g., in-person, phone, video) with time/date noted for each scale. More information will be forthcoming on how to transfer paper documentation to SLATE device and/or EDC.

The PRO assessments are described below after the Rater Training Requirements.

Rater Training Requirements

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

The sponsor, in conjunction with the selected rater training vendor, 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 and, if they meet established requirements, certified accordingly. Individual exceptions to these requirements may only be approved by the sponsor via the rater training vendor.

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 efficacy raters will not have access to the results of other study assessments or medical records for the subject, will not participate in the care, or management of the subject, in order to maintain the study blinding. Therefore, study sites will identify and submit appropriate personnel for rater qualification and training, taking into account their site roles and the blinding considerations described in Protocol Section 5.8.

Subject Dosing Diary

Subjects will complete a dosing diary. The time a new syringe is started (with or without a loading dose), stoppage in therapy (e.g., vial change-out, shower), pump alarms (e.g., occlusion alarm), blinded oral study drug times and doses, and CD/LD IR tablets self-administered by the subject during the study as possible rescue therapy should be recorded for 3 consecutive days prior to any study visits (as specified in Section 2). Additionally, all instances during the Treatment Period of the administration of oral CD/LD IR tablets as rescue therapy should be documented in the dosing diary (i.e., not only the 3 days prior to study visits). Rescue therapy can be administered in half or whole tablets of CD/LD IR, as needed (e.g., ½ tablet, 1 tablet, 1 ½ tablet, 2 tablets). Completed dosing diaries should be reviewed by the investigators at every study visit. Half tablets are not allowed in the case of pump malfunction when the blinded study drug infusion and blinded study drug capsules should be stopped.

Note: Subjects should be reminded with a phone call at least 4 days prior to each visit to complete the dosing diary and to reinforce the importance of dosing diary completion. If during the study, the subject incorrectly completes the dosing diary, they should receive re-training on dosing diary completion.

Parkinson's Disease Diary

PD Diary Subject Training and 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 V1.

PD Diary Concordance Assessment

Following the initial PD Diary training during V1, the subject will complete a PD Diary on the touch (handheld) device over a minimum of 3 hours for a concordance evaluation while he/she is in the clinic at V1 as shown in Section 2.1. 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 on the Slate (tablet) device 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 investigator or designee's discretion. If the concordance is less than 75%, the subject will undergo re-training of PD Diary completion and may repeat the concordance evaluation one more time before completing the PD Diary at home.

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-hour period 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 3 consecutive days prior to V2, and prior to each study visit specified in Section 2. Subjects who do not meet the required minimum 2.5 hours of "Off" time on average (with a minimum of 2 hours of "Off" time per day) across the 3 consecutive days prior to V2, may repeat the PD Diary for 3 additional consecutive days during the Screening Period. If the criterion is still not met after this, subjects must screen fail.

The PD Diary will also be completed for 3 consecutive days (which should be started at least 4 days prior to V6, i.e., PD Diaries need to be completed prior to Day –1) to confirm eligibility before randomization. Subjects who do not meet the required minimum of at least 2 hours of "Off" time each day for 3 consecutive days before V6 (Randomization) must be prematurely discontinued from the study.

Note: Subjects should be reminded with a phone call at least 4 days prior to each visit (at least 5 days prior to V6) to complete the PD Diary and to reinforce the importance of PD Diary completion. A

minimum of 44 out of 48 entries are required for each 24-hour period for a valid entry. If during the study, the subject incorrectly completes the PD Diary, they should receive re-training on PD Diary completion.

EQ-5D-5L

The 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 the country-specific weighted scoring algorithm for the United States (US). The index value for the 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.

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. 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 to a proprietary cloud system for processing at the time of recharging.

Subjects will be required to wear the PKG watch (reference the currently approved manufacturer's directions) from V1 to Day 85 (V13) in the countries where allowed. In the US only, the PKG watch is approved by the US Food and Drug Administration for use by PD subjects from 46 – 83 years of age. The AbbVie TA MD should be consulted if, in the investigator's opinion, there are circumstances that might interfere with the use of the PKG device (e.g., religious reasons, atopic dermatitis).

During the Screening Period (i.e., 6 - 8 days before V3), 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 habitual first dose of oral PD medications.

Mini-Mental State Examination

The MMSE is a brief 30-point questionnaire administered by a qualified rater, that provides a quantitative measure of cognitive 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 total score ≥ 24 at V1 to be eligible for study participation. A qualified rater will administer the MMSE.

Movement Disorder Society-Unified Parkinson's Disease Rating Scale

The MDS-UPDRS is an investigator-used rating tool to follow the longitudinal course of PD. Study sites should make every effort 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 a qualified 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.

At all indicated visits specified in Section 2, a complete MDS-UPDRS (Parts I - IV) should be administered in the subject's best "On" time and, if possible, at the same time of day at each visit throughout the study.

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.

Any subject who has suicidal ideation with plan within the last year, either via answering "yes" to Question 4 and/or Question 5 to the suicidal ideation portion of the C-SSRS, or via clinical interview, will be evaluated immediately by the investigator. The AbbVie TA MD must also be notified. In addition, if the subject expresses suicidal ideation at any time during the study, the investigator and the AbbVie 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 as shown in Section 2. The Baseline/Screen version will be administered at V1, while the Since Last Visit version will be administered at all subsequent visits.

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 is 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 Disease Sleep Scale-2

Although several scales exist to evaluate sleep disturbances, only 3 are endorsed and recommended by the Movement Disorders Society. One such scale is the PD Sleep Scale (PDSS), which has been modified to 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, rapid eye movement behavior disorder, 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.

The PDSS-2 will be administered via telephonic interview by a qualified blinded central rater at the visits specified in Section 2.

Parkinson's Disease Questionnaire-39 item

The 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.

The PDQ-39 will be administered via telephonic interview by a qualified blinded central rater at the visits specified in Section 2.

Infusion Site Rotation Tool

To help guide their infusion site rotation pattern and help prevent overuse of an infusion site area, subjects will use an Infusion Site Rotation Tool. Subjects will track each infusion site by recording the date corresponding to the abdomen location used. Site personnel will train subjects on this tool on or prior to Day 1. Subjects should receive re-training on using the tool as needed (e.g., if they are not correctly recording or forgetting to record infusion sites used).

Exit Interview

Subjects (and caregivers, if applicable) will be asked to provide answers to brief questions about their study participation and experience, including their estimate of whether they were assigned to ABBV-951 solution or placebo solution and the reason for their choice. Study sites should ensure that subjects and caregivers independently provide the responses and that this interview is the last activity of the last study visit to minimize bias. The site will record the responses into EDC.

3.10 Height and Weight

Height will be measured at V1 only; weight will be measured at the visits specified in Section 2. The subject should not wear shoes during either measurement.

See Section 7.2 for criteria for PCS weight values.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, height and weight measurements may be performed by the subject or caregiver as needed and recorded in the source. 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.

3.11 Vital Signs

Vital signs will be collected both supine and standing for orthostatic assessments. For supine vital signs, blood pressure and pulse rate will be measured after the subject has been supine for at least 5 minutes. For standing 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. Three sets of orthostatic vital sign assessments will be collected approximately 20 minutes apart at Visit 5. Vital signs on Day 1 (V6) will be measured before randomization and also approximately 2 hours after initiation of blinded study drug administration prior to the end of the visit.

See Section 7.2 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 via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed and recorded in the source. 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.

3.12 Physical Examination

A complete physical examination will be performed at the visits shown in Section 2. The physical examination performed at 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 V3 will be recorded as AEs.

3.13 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 V5 will serve as the Baseline for clinical assessment. After randomization, any significant neurological findings 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

3.14 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 (V6) will be recorded approximately 2 hours after initiation of the blinded study drug administration.

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 V6 or V3 [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. The 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 this 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 Clinical Laboratory Tests

Samples for clinical laboratory tests will be collected at the visits specified in Section 2. 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 Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Absolute platelet count Mean corpuscular hemoglobin Mean corpuscular volume concentration (MCHC) Prothrombin time (PT) Activated partial thromboplastin time	Blood urea nitrogen (BUN) Creatinine[a] Creatine phosphokinase Total bilirubin Serum glutamic pyruvic transaminase Serum glutamic-oxaloacetic transaminase Lactate dehydrogenase (LDH) Gamma-glutamyl transpeptidase Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Total protein Albumin Glucose Sodium bicarbonate/CO_2 Chloride Triglycerides Cholesterol Magnesium <u>Special Laboratory Tests[b]</u> Vitamin B_6 Vitamin B_{12} Folic acid Methylmalonic acid (MMA) Homocysteine	Specific gravity Ketones pH Protein Glucose Blood Bilirubin Microscopic examination, if indicated

eGFR = estimated glomerular filtration rate

a. eGFR (i.e., estimated glomerular filtration rate) 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 V1, prior to randomization, and Day 85 (V13). An abnormal vitamin B_{12} level of questionable clinical significance (indeterminate or low normal results at V1), require 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.

The investigator must evaluate all laboratory abnormalities that occur during the study to determine whether they indicate a new disease process, or 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 Section 7.1.

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 (V6) urine pregnancy test will be collected prior to randomization and initiation of blinded study drug administration.

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 specified in Section 2. If a urine pregnancy test is positive, the results should be confirmed with a serum human chorionic gonadotropin (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 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

The urine pregnancy test may be dispensed via direct-to-patient (DTP) courier, or a family member may pick the test up from the site, if locally allowed and authorized. Negative urine pregnancy test must be recorded by the site prior to a subject's next dose of study drug (open label CD/LC IR or blinded study drug). If a urine pregnancy test is positive, the results should be confirmed with a serum hCG test. This may be performed by a local laboratory.

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 non-fasting status will be recorded in study source documentation.

Urinalysis

Urinalysis will be completed 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.

3.16 Drug Screen

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

Urine specimens will be tested at V1, as shown in Section 2.1, for the presence of drugs of abuse. 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 investigator's opinion, 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.*

3.17 Study Drug Prescription Record

Starting at V2, with the Oral CD/LD Stabilization Period, through the end of the study as shown in Section 2, the subject's CD/LD IR regimen (number of tablets at each administration and dosing frequency) reached at the end of the Oral CD/LD Stabilization Period, pump settings (continuous infusion rate in mL/hour and loading dose in mL) and blinded oral study drug regimen should be recorded at the conclusion of each visit on the study drug prescription record.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, this study activity may be performed in the subject's home by the HHN or site staff. The Study Drug Prescription Record is eligible for completion by interview at V3, V4, and V7, V8, V9, V10, V11, and V12. In this situation, the DTP courier will confirm IP is delivered in good condition, and the HHN or site staff will review dosing and review the dosing regimen. During the Randomization Period, there is potential for the site staff or HHN to update pump settings in subject's home under investigator direction and delegation. Pump setting changes cannot be performed by the subject or caregiver.

3.18 PM-PDSC Pump Delivery System Training

AbbVie personnel, or its delegate, will train the staff at each site how to calculate each subject's LD equivalent, 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 Phillips-Medisize - Parkinson's Disease Subcutaneous (PM-PDSC) Pump Delivery System by (i) loading the study drug solution 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 pump instructions for use for patients and the pump instructions for use for clinical study personnel.

As part of study eligibility, subjects and caregivers (if applicable) will receive training at Screening Visit 1 (V1) on the PM-PDSC Pump Delivery System (e.g., infusion pump, infusion set, syringe, vial, vial adapter, and the insertion of the cannula). In addition to training, subjects will receive training materials for reference. To remain eligible for study participation, the investigator or designee must assess that the subject and caregiver, if applicable, have demonstrated understanding and correct use of the delivery system, including insertion of the cannula into the subject's abdomen.

Subjects and caregivers (if applicable) may continue to be trained by site staff or nurses contracted by the sponsor on use of the PM-PDSC Pump Delivery System. These nurses must be trained on how to use the PM-PDSC Pump 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 PM-PDSC Pump 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 PM-PDSC Pump Delivery System. The home health care

nurse will record the subject's answers and provide these to the study site for review. Subjects may also have access to an after-hours call center for additional PM-PDSC Pump Delivery System support.

3.19 Study Drug and PM-PDSC Pump Delivery System Dispensation and Return

Open-label CD/LD IR tablets and blinded study drug (solution for infusion and capsules) will be dispensed throughout the study. Subjects and/or caregivers may visit the site for CSCI solution dispensation and return outside of the scheduled visits. The PM-PDSC Pump Delivery System, including the infusion set and other accessories, will be dispensed as needed. AbbVie personnel or its delegates will train clinical study personnel on the distribution and reconciliation details.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
    - Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of PROs, urine pregnancy tests, PD-PMSC ancillary supplies). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19-related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

The subject and/or caregiver will be instructed on how to return all study drug, devices, and ancillaries. Clinical study personnel will document compliance.

3.20 Subject Withdrawal from Study

All attempts must be made to determine the last day of study drug and the reason(s) for discontinuation of study drug or study participation. The information will be recorded on the appropriate 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 the subject decides to continue participation in the study.

3.21 Home Healthcare Service Due to COVID-19 Pandemic

In addition to the HHN service to support PM-PDSC system training for the study, subjects may be offered the option for the HHN to perform delegated study activities. Study procedures conducted in the home setting may include those indicated in Sections 2 and 3. These activities may include, but are not limited to, programming the study pump to adjust the flow rate under the delegation of the investigator, verifying the supply of study drug, PM-PDSC Pump Delivery System, and ancillaries.

This option can only be offered in countries and sites that comply with local regulatory and IRB/IEC requirements for homecare. Any pre-requisite submissions or notifications to the site IRB/IEC and local competent health authority should be made and approvals must be obtained prior to implementation of home infusions.

For Studies with IP Infusions:

Finally, it is recommended that medical personnel entering a subject's home adhere to local health regulations during the COVID-19 pandemic, such as the use of personal protective equipment (PPE), as required.

Protocol deviations must be recorded per AbbVie's standard process.

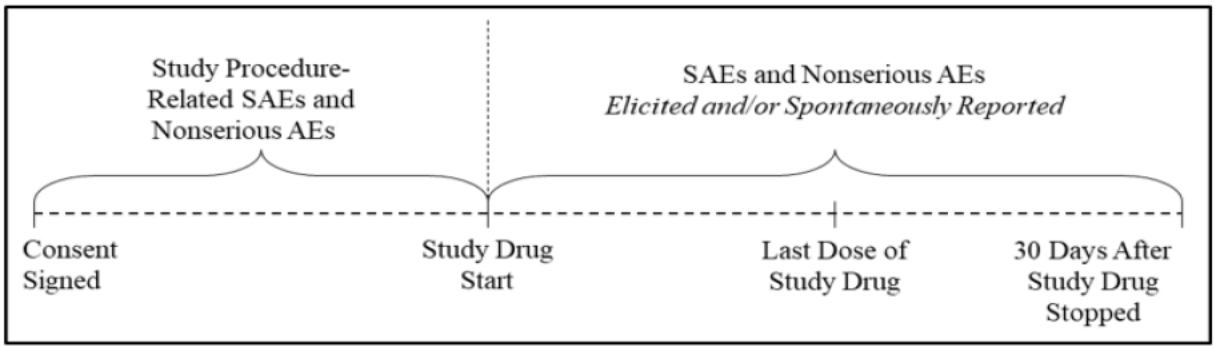
If the home visits will not be performed by site personnel or the sponsor-provided HHN, the site may be responsible for selecting a vendor, contracting with a vendor, and for ensuring continued compliance with the terms of the Clinical Study Agreement.

Individuals performing home visits need to be added to the delegation log. If utilizing a vendor, the delegation of authority log provided by the vendor may be required to be used for the nurses supplied by the vendor. The principal investigator must ensure that any staff performing drug infusions are qualified and trained to do so per local regulations.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All SAEs and nonserious adverse events (AEs) that could be related to study procedures will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration (V3) until 30 days after discontinuation of study drug 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 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 non CRF 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
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 Therapeutic Area Medical Director (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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

COVID-19 infections should be captured as AEs. 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:

- 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 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 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (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.

5.2 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 appropriate subsequent treatment with the subject.

6 References

1. US Dept of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. December 1999.

7 Appendices

7.1 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 (white blood cell count 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)
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)

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
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
Hypercalcemia		**Corrected Serum Calcium of:**				
	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
Hyperglycemia		**Fasting Glucose Value**				
	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

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
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
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
Hypocalcemia		**Corrected Serum Calcium**				
	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

7.2 CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGN AND WEIGHT VALUES

Variable Measured	**Potentially Clinically Significant (PCS) 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
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
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