Study Procedures and Assessments
Protocol Number: CTH-302

Study: An Open-Label, Randomized, Crossover Trial utilizing a Single-Blinded Rater to evaluate APL-130277 compared to s.c. Apomorphine in Levodopa Responsive Subjects with Parkinson's Disease Complicated by Motor Fluctuations

Screening Visit 1

This is the first of two Screening Visits. The procedures and assessments completed at this visit will help study doctors and staff members determine if you can participate in this study.

This visit involves:

- Reading and signing a written informed consent form
- Review of the entry criteria
- Movement disorders assessment
- Parkinson's Disease (PD) assessment

Screening Visit 2

This is the second and final Screening Visit. The procedures and assessments completed at this visit will help study doctors and staff members determine if you can participate in this study.

Please withhold your normal Levodopa dose and any other PD medication on the morning of this visit (you can take it before midnight prior to this Screening Visit). You will then receive your Levodopa dose at the clinic visit.

This visit involves:

- Review of the entry criteria*
- Review of medical history and demographics
- Complete physical exam, including oropharyngeal exam
- BMI, weight and height assessments
- Vital signs measurements
- Electrocardiogram assessment
- Collection of clinical laboratory tests
- Mini Mental State Examination (MMSE) assessment
- PD assessment (before and after Levodopa dosing)*
- Participant "OFF" versus "ON" training*
- Mental and behavioral assessments
- Take dose of Levodopa and confirm a response to medication*
- Movement disorders assessments (before Levodopa dosing and 30 minutes after)*
- Confirmation of "OFF" or "ON" by Investigator and participant*
- Post-dose assessment of Dyskinesia
- Impulsive-compulsive disorders assessment
- Review of side effects or adverse events
- Review of current and previous medication

All procedures scheduled for SV2 can be completed at SV1 except procedures with* **must be completed at SV2.*

PART A: Titration Visits

You are requested to take several doses of the study drug in order of increasing strength to determine which dose works best for you when treating your "OFF" episodes. This process is referred to as 'Titration'. You will be assigned two study drugs (APL-130277 film or apomorphine injection), and will undergo titration for each study drug at a time. The effective dose of each study drug will be used to treat your "OFF" episodes in PART B.

Titration Visit 1 for both study drugs:
You will be required to arrive at the clinic in an "OFF" state. You should stop taking your PD medication by midnight the night before, and then withhold any other PD medications before you take the study drug.

APL-130277:
If the first dose on Titration Visit 1 is **not** effective in achieving a full "ON" response, you will resume your regular PD medications. You will take an increased dose of the study drug the next morning at home, and will continue to repeat the process until you reach the most effective dose to treat your "OFF" episodes. The study staff will call to monitor your response every day. Once you reach the most effective dose, you will be asked to return to the clinic. You will also complete a daily home dosing diary.

Apomorphine Injection:
If the first dose is **not** effective, you will receive an increased dose an hour later. This may be repeated once more on Titration Visit 1 (up to a total of 3 doses). If the third dose is not effective, you will be asked to return to the clinic the following day to receive up to 2 further doses.

This visit involves:

- Randomisation to the order of treatment you will receive (Titration Visit 1 only)
- Abbreviated physical exam, including oropharyngeal and injection site exam
- Vital signs measurements
- Electrocardiogram assessment
- Movement disorders assessments (before taking the study drug and at 15, 30, 60, 90 and 120 minutes after)
- In-clinic dosing of study drug
- Confirmation of "OFF" or "ON" by Investigator and participant
- Post-dose assessment of Dyskinesia
- Study medication dispensation for home dosing/collection
- Receiving/returning home dosing diary
- Mental and behavior assessment

PART A: Titration Visits - continued

- Impulsive-compulsive disorders assessment
- Review of any side effects or adverse events
- Review of previous and current medication

PART B: Clinic Visit 1, 2, 3, 4, 5 and 6 (Days 1, 14, 28, 33, 47 and 61)

Please remember to stop taking your PD medications by midnight on the evening prior to these visits, and do not take these medications on the morning of these visits.

You will receive a phone call between each of these visits to review any side effects, and medications you have taken or are taking.

You will complete a daily home dosing diary between visits and an expanded home dosing diary for 3 continuous days before each visits. You will be asked to bring both of these diaries to each of these visits, as well as any used and unused study drug.

This visit involves:

- Randomisation to the order of treatment you will receive (Clinic Visit 1 only)
- Abbreviated physical exam including oropharyngeal and injection site exam
- Vital signs measurements
- Electrocardiogram assessment
- Collection of clinical laboratory tests
- Movement disorders assessments (before taking the investigational drug and at 15, 30, 60, 90 and 120 minutes after)
- In-clinic dosing of study drug
- Confirmation of "OFF" or "ON" by Investigator and participant
- Post-dose assessment of Dyskinesia
- Receiving self-administration training, if needed
- Dispensation of study medication§
- Returning study medication‡
- Home dosing diary training**
- Receiving home dosing diary§
- Returning home dosing diary‡
- Mental and behavior assessments
- Dyskinesia questions*
- PD questionnaire†

PART B: Clinic Visit 1, 2, 3, 4, 5 and 6 (Days 1, 14, 28, 33, 47 and 61) - continued

- Patient global impression assessments†
- Clinical global impression assessments†
- Caregiver interview (if applicable)†
- Impulsive-compulsive disorders assessment‖
- Quality of life assessment†
- Treatment satisfaction questionnaire for medication*
- Treatment preference questionnaire (Clinic Visit 6 only)
- Review of any side effects or adverse events
- Review of previous or current medications
- Blood sample collection (certain sites only)‡

*Clinic Visits 3 and 6 only
**Clinic Visits 1 and 4 only
†Clinic Visits 1, 3 and 6 only
‡Clinic Visits 2, 3, 5 and 6 only
§Clinic Visits 1, 2, 4 and 5 only (Visits 2 and 5 only: unused study drug [which was dispensed from IXRS at Clinic Visit 1 and 4, respectively] will be resupplied to the participant)
‖Clinic Visits 1, 3, 4 and 6 only

End of Study Visit

This is the final visit of the study. Please remember to bring any used and unused study drug to this visit, if applicable.

This visit involves:

- Complete physical exam, including oropharyngeal and injection site exam
- Weight assessment
- Vital signs assessment
- Electrocardiogram assessment
- Collection of clinical laboratory tests
- Mental and behavioral assessment
- Review of side effects or adverse events
- Review of previous or current medication

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