A Phase 2 Study to Examine the Safety, Tolerability and Efficacy of APL-130277 in Patients with Parkinson's Disease

PROTOCOL NUMBER:	CTH-105
IND	N/A
PROTOCOL DATE:	10 September 2014
SPONSORED BY:	Cynapsus Therapeutics Inc.

1. SIGNATURES OF AGREEMENT FOR PROTOCOL

[redacted]

Sept 10/2014
Date

Chief Medical Officer
Cynapsus Therapeutics Inc.
828 Richmond Street West
Toronto, Ontario Canada

[redacted]

Sept 10/2014
Date

President and CEO
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Sept. 10/2014
Date

Study Clinical Monitor
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2. EMERGENCY CONTACT INFORMATION

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3. INVESTIGATOR APPROVAL STATEMENT

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Cynapsus Therapeutics Inc. (Cynapsus) during the study. I will adhere to all Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), and other applicable regulations and guidelines regarding clinical trials on a study drug during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Protocol
A Phase 2 Study to Examine the Safety, Tolerability and Efficacy of APL-130277 in Patients with Parkinson's Disease

Protocol: 10 September 2014
Version: 2.0

4. PROTOCOL SYNOPSIS

TITLE	**A Phase 2 Study to Examine the Safety, Tolerability and Efficacy of APL-130277 in Patients with Parkinson's Disease.**
STUDY PHASE	Phase 2
OBJECTIVES	The primary objective of this study is to evaluate the efficacy, tolerability and safety of single treatments of APL-130277 in 16 patients with Parkinson's Disease (PD).
NUMBER OF PATIENTS	16 patients will be enrolled.
PATIENT POPULATION	**Inclusion criteria** 1. Male or female ≥18 years of age. 2. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria. 3. Receiving stable doses of L-dopa +/- other adjunctive PD therapy for at least 4 weeks before study participation. 4. At least one OFF episode per day and a total daily OFF time of ≥ 2 hours duration. 5. Experience predictable OFF episodes in the morning on awakening prior to receiving morning dose of levodopa. 6. Stage I to III on the Hoehn and Yahr scale in the "ON" state. 7. If female and of childbearing potential, must agree to use one of the following methods of birth control: o Oral contraceptive; o Contraceptive Patch; o Barrier (diaphragm, sponge or condom) plus spermicidal preparations; o Intrauterine contraceptive system; o Levonorgestrel implant; o Medroxyprogesterone acetate contraceptive injection; o Complete abstinence from sexual intercourse; o Hormonal vaginal contraceptive ring; or o Surgical sterilization or partner sterile (must have documented proof). 8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study. 9. Able to understand the consent form, and to provide written informed consent. **Exclusion criteria** 1. Atypical or secondary parkinsonism 2. Changes in L-dopa or other PD drug dosing regimens 4 weeks before the screening visit. 3. Past treatment with any form of apomorphine within 30 days of Dosing Day 1 (patients who stopped apomorphine for reasons other than lack of efficacy OR tolerability issues may be considered for the trial). 4. Female who is pregnant or lactating. 5. Contraindications to APOKYN or hypersensitive to apomorphine hydrochloride or any of the ingredients of APOKYN (notably sodium metabisulfite), or Tigan®. 6. Participation in any other clinical trial within 14 days of the screening

	visit. 7. Receipt of any investigational (i.e., unapproved) medication within 30 days of the screening visit. 8. Currently taking, or likely to need to take at any time during the course of the study, any 5HT3 antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron). 9. Currently taking dopamine antagonists or depleting drugs excluding anticholinergics and/or antihistamines with anticholinergic effects. 10. Drug or alcohol dependency in the past 6 months. 11. Clinically significant orthostatic hypotension. 12. Malignant melanoma or a history of previously treated malignant melanoma within 5 years. 13. Clinically significant medical surgical or laboratory abnormality in the judgment of the investigator. 14. Psychiatric disorder, including but not limited to dementia or any disorder that, in the opinion of the Investigator requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult. 15. Dementia that precludes providing informed consent. 16. Potential for lack of compliance and follow-up in the judgment of the investigator. 17. Any other condition, current therapy, or prior therapy (within 30 days of the screening visit), which, in the opinion of the Investigator, would make the subject unsuitable for the study. 18. Previous neurosurgery for PD. 19. Donation of blood or plasma in the 30 days prior to dosing. 20. Presence of cankers or mouth sores.
STUDY DESIGN	This multicenter Phase 2 open-label study is designed to determine the safety, tolerability and efficacy of a dose of APL-130277 needed to induce an on response in patients with Parkinson's disease. After a screening visit (Visit 1), patients will be supplied with Tigan® (300 mg tid orally) which is to be started on Day -3 and they will be asked to return to clinic at Day -1 (Visit 2) to have pre-dosing assessments of safety completed. Patients will be asked to take their last dose of LD no later than 10 PM on the evening of Day -1 and prepare to return to clinic the morning of Day 1. Alternatively, patients may be monitored in the clinic overnight if such facilities exist and the patient consents. On Dosing Day 1 (Visit 3), patients who are in an OFF state will be administered a starting dose of 10mg APL-130277. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from initial dosing and does not experience protocol defined orthostatic hypotension, they will receive the 15mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. The patient will be asked to take their last dose of Levodopa no later than 10 PM on the evening before Dosing Day 2 (Visit 4), and prepare to return the morning of Dosing Day 2 for dosing. At clinical sites where this is a possibility, patients, at their request, may stay overnight in the clinic.

	Patients will be seen on the morning of Dosing Day 2 (Visit 4), perform pre-dosing safety assessments and clinical assessments to determine their OFF status. Patients who are in an OFF state will be treated as follows: If there was **no** response with either dose on Dosing Day 1: • Administer: 20mg APL-130277. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience protocol defined orthostatic hypotension, they will receive the 25mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. If there was a response with either dose on Dosing Day 1: • Administer the dose that elicited a response on Dosing Day 1. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined in Section 12.6, they will receive the next higher dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. Patients who responded to the same dose at Dosing Day 1 and Dosing Day 2 (Visits 3 and 4) will be considered complete from a dosing perspective, and proceed to Day 7 (Visit 6). Patients who responded to a new dose at Visit 4, or who did not respond to either dose at Visit 4 will proceed to Dosing Day 3 (Visit 5). Patients will be asked to take their last dose of Levodopa no later than 10 PM on the evening before Dosing Day 3 (Visit 5), and prepare to return the morning of Dosing Day 3 for dosing. At clinical sites where this is a possibility, patients, at their request, may stay overnight in the clinic. If patients are evaluated to be in an OFF state, they will receive either the next higher dose of APL-130277, or the dose at Day 2 (Visit 4) that elicited an ON response. Procedures at Dosing Day 3 (Visit 5) will be identical to that of Dosing Day 2 (Visit 4). If the first dose administered at the visit is 30mg of APL-130277, the patient will proceed to the follow-up visit following a 90 minute assessment of response and resolution of the OFF episode with levodopa if required. Dosing Days are not required to be sequential, but all dosing must be

	completed within 7 days. Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day. Patients will return to clinic on Day 7 for a full safety evaluation.
INVESTIGATIONAL DRUG	APL-130277 (10mg, 15mg, 20mg, 25mg and 30mg sublingual strips)
REFERENCE PRODUCT	N/A
TREATMENT REGIMENS	Dose titration from 10mg upwards
CONCOMITANT AND CO-ANALGESIC TREATMENT	Tigan®, (300 mg tid orally) to overcome the nausea associated with administration of APL-130277.
PROHIBITED TREATMENT	Treatment with any form of apomorphine within 30 days of Dosing Day 1 Any 5HT3 antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron). Dopamine antagonists or depleting drugs excluding anticholinergics and/or antihistamines with anticholinergic effects.
STUDY DURATION	It is anticipated that from screening until Day 7 (study completion) will take a maximum of 28 days. Dosing must be completed within 7 days.
INVESTIGATIVE SITES OR COUNTRIES	This is a multicenter trial run at 4 or more clinical sites in the United States of America.
STUDY ENDPOINTS	1. Safety Evaluation of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including body temperature and weight), and adverse events 2. Tolerability: Percent of subjects that complete trial and experience an ON episode 3. PK: Pharmacokinetic profile, including: Cmax, Tmax, λz, t1/2, AUC, Kel 4. Number of patients with resolution of an OFF episode to an ON state as confirmed by investigator at 15, 30, 45, 60 and 90 minutes after dosing 5. Time to ON from time of dosing 6. Percent change in MDS-UPDRS Motor Score from pre-dose to 15, 30,45 60, and 90 minutes after dosing 7. Duration of ON response.
STATISTICAL METHODS SUMMARY	A power calculation has not been applied in this clinical trial. Based on historical data with apomorphine and the known bioavailability of APL-130277, it is estimated that 16 patients will be sufficient to predict the starting dose needed for the registration trial.

5. STUDY DESIGN FLOW CHART

Procedures	Screen[1]	Phone Call[2]	Baseline Day	Dosing Day 1	Dosing Day 2	Dosing Day 3[15]	F/U[13]
Study Visit	Visit 1	T1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Day	-21 to -4	-4	-1	1	2	3	7
Outpatient Visit[3]	X		X[3]	X[3]	X[3]	X	X
Written and Reconfirmation of Informed Consent	X		X	X	X	X	X
Review Entry/Restriction Criteria	X		X	X	X	X	
Medical History/Demographics	X						
Complete Physical Exam[4]	X						X
Abbreviated Physical Exam[5]				X	X	X	
Anti-nausea medication (starts on day-3)	X		X	X	X	X	
BMI, weight and height[6]	X						X
Vital Signs (BP, HR, RR and Temp.) [7, 14]	X			X	X	X	X
12-Lead ECG[8]	X			X	X	X	X
Clinical Laboratory Tests[9]	X						X
Hoehn and Yahr	X						
MDS-UPDRS Motor Function[10, 14]	X		X	X	X	X	
Clinical Confirmation of OFF or ON[11, 14]				X	X	X	
Dosing of APL-130277				X	X	X	
Blood Draw for Study Drug PK[12, 14]				X	X	X	
AEs/SAEs			X	X	X	X	X
Conclusion of Participation							X

[1] All screening procedures to be conducted within 21 days prior to dosing (Day 1).
[2] Reminder phone call to patient to start their Tigan 300 mg tid on the morning of Day -3.
[3] Patients may be monitored in the clinic overnight before Dosing Visits if such facilities exist and the patient consents.
[4] Physical examination to include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including mouth; musculoskeletal system; central and peripheral nervous system; and skin.
[5] Abbreviated physical exam to include head-eyes-ears-nose and throat; heart; lungs; abdomen; and skin; to be done at t = 0 (just prior to dosing) and at t = 1.5 post dosing (each dose) at Visits 3-5
[6] Both height and weight captured at Screening Visit to calculate BMI; only weight captured during Day -1, Day 1, and Final Visit.
[7] Vital signs will be assessed at Screening Visit, Visits 3-5 at t = 0 hrs (just prior to dosing) and at t =0.25, 0.5, 0.75, 1.0, 1.5, hrs post dosing and at Visit 6; Blood pressure to be measured sitting and standing (measured within 3 minutes of standing) at all time points at Visits 3-5
[8] Triplicate 12-lead ECG at screening; single ECGs at t = 0 (just prior to dosing) and at t = 0.5 post dosing (each dose) at Visits 3-5and a single ECG at Visit 6
[9] Blood collection for clinical laboratory tests will occur at Screening Visit and on Visit 6.
[10] MDS-UPDRS Motor Function at Visits1 and 2, and Visits 3-5 at t = 0 (just prior to dosing), and at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs post dosing
[11] Investigator confirmation of OFF or ON at Visits 1 and 2, and Visits 3-5 at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs

post dosing
[12] Blood collection for APL-130277 pharmacokinetic (PK) analyses will occur at select sites only at Visits 3-5 at t = 0 (just prior to dosing) and at t = 10, 20, 30, 45, 60 and 90 minutes after each dose administered
[13] The follow-up visit will be conducted for every patient dosed with APL-130277, and the timing of the Visit can be as soon as the day immediately following last dosing
[14] Suggested Sequence of Assessments Post-Dosing: PK blood draws – UPDRS – Assessment of OFF/ON – Vitals – ECGs
[15] Dosing must be completed within 7 days

Note: Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day. All dosing must be completed within 7 days.

6. TABLE OF CONTENTS

7. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APOKYN	apomorphine hydrochloride injection
API	active pharmaceutical ingredients
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CAS	Chemical Abstracts Service
Cynapsus	Cynapsus Therapeutics Inc.
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CNS	central nervous system
CRA	Clinical Research Associate
CRF	case report form
CSA	clinical study agreement
D1-like	Dopamine receptor subtype D1
D2-like	Dopamine receptor subtype D2
DCC	data coordination center
DMP	Data Management Plan
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA	Ethylenediaminetetraacetic acid
ETV	Early Termination Visit
FCC	Food Chemicals Codex
FDA	Food and Drug Administration
g/mol	Grams per mole
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IUPAC	International Union of Pure and Applied Chemistry
K_{el}	Apparent first-order terminal elimination rate constant
L-Dopa	L-3,4-dihydroxyphenylalanine
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration

MedDRA	Medical Dictionary for Regulatory Activities
MDS-UPDRS	Movement Disorder Society (MDS) Unified Parkinson's Disease Rating Scale
NF	National Formulary
PD	Parkinson's Disease
PH	logarithmic measure of hydrogen ion concentration
PKa	negative base-10 logarithm of the acid dissociation constant of a solution
RBC	red blood cell
REB	Research Ethics Board
SAD	single-ascending dose
SAE	serious adverse event
s.c.	Subcutaneous
SL	sublingual
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
US	United States
USP	U.S. Pharmacopeial Convention
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

8. INTRODUCTION

8.1 Background

Apomorphine is a non-ergot dopamine agonist that binds to D1-like and D2-like receptors. First used as a treatment for Parkinson's disease (PD) as early as 1951, its clinical use was first reported in 1970 although its emetic properties and short half-life made oral use impractical. A later study found that combining the drug with 10mg domperidone improved results significantly (1-3).

APOKYN (apomorphine hydrochloride injection, Appendix I) is the first and only prescription medicine that reverses OFF episodes (end-of-dose wearing-OFF and unpredictable ON-OFF episodes) associated with advancing PD. APOKYN, which is indicated for the acute, intermittent treatment of hypomobility, OFF episodes associated with advanced Parkinson's disease, has been studied as an adjunct to other PD medications. Therapeutic use in Parkinson's disease is effective because of the drug's strong dopaminergic action. When administered subcutaneously, apomorphine is the most effective dopamine agonist. Within 3-20 minutes of injection, apomorphine demonstrates a magnitude of effect (ability to convert the patient with Parkinson's disease to the ON state) that is faster than L-Dopa. The effects of a single subcutaneous injection last for 60-90 minutes. Apomorphine can be used in combination with L-Dopa. L-Dopa dosing may need to be readjusted (decreased) to reduce dopa-induced dyskinesias and "wearing-off" periods (4).

Subcutaneous injection of apomorphine was developed to avoid first-pass metabolism. The total daily dose can range up to 20-25mg/daily. Trimethobenzamide hydrochloride (Tigan®), structurally similar to the dimethylaminoethoxy antihistamines, may be administered to lessen the symptoms of nausea and vomiting that are caused by apomorphine's peripheral dopaminergic action. Patients on chronic apomorphine treatment may be able to discontinue Tigan® co-administration after about 2 months without recurrence of the adverse effects of apomorphine.
Cynapsus is developing APL-130277, an easy-to-administer sublingual, fast-acting thin film strip formulation of apomorphine.
APL-130277 is a bilayer film containing apomorphine hydrochloride in 10, 15, 20, 25 and 30 mg dose strengths. APL-130277 is intended for fast sublingual absorption for use in rescue therapy for acute intermittent OFF episodes experienced by Parkinson's patients.

8.2 Clinical Experience

This is fifth in-man study for APL-130277. Previous studies, CTH-101-104 were performed in healthy volunteers.

The studies are summarized in considerable detail in the Investigator Brochure. Adverse events were those expected to be seen with apomorphine, with the most common adverse being sleepiness, dizziness and nausea. No dose limiting side effects were encountered.

The healthy volunteer studies confirmed the method of administration, allowed further refinement of the formulation and confirmed PK comparability of APL-130277 to APOKYN. The CTH 103 and 104 study PK results demonstrated dose proportionality of the doses of APL-130277 tested (10mg,15mg, 25mg) and that the 25mg dose is sustained over an extended period of time (162 minutes) above the minimal efficacious plasma concentration of apomorphine (approximately 3ng/ml), believed to be a level demonstrating symptomatic relief of "OFF" symptoms. The Tmax for the 25mg dose of APL-130277 was approximately 40 minutes, which was similar for the 10mg and 15mg doses of APL-130277. The rapid uptake of apomorphine in the APL-130277 strips is comparable to that described in the Apokyn® label (i.e. between 10 and 60 minutes).

8.3 Summary of Potential Risks and Benefits

Given that APL-130277 uses the same active pharmaceutical ingredient as APOKYN, and that the pharmacokinetic profile is very similar between the sub-lingual strip and the s.c. injection, Cynapsus believes that the risks associated with the drug will be the same as those seen in the APOKYN Product Insert (Appendix I), except for the significant injection site reactions. The use of 10mg as a starting dose for CTH-105 is based on safety, tolerability, PK data obtained from the healthy subject trials (CTH101-104). It is assumed that the bioavailability of APL-130277 will be consistent in CTH-105 with that found in previous experience with APL-130277, and that the doses of 15mg, 25mg and 30 mg should be comparable to 3mg, 4mg and 5 mg of s.c. apomorphine. These doses have been extensively studied and have been found to be safe and well-tolerated (as shown in the APOKYN Product Insert in Appendix 1).
The buffer contained in the inactive layer of APL-130277 is designed to mitigate potential irritation of the oral mucosa seen in other buccal formulations of apomorphine as well as assist in maintaining a stable pH and optimal absorption kinetics. There is still a risk of local irritation and the study will closely assess that potential AE. The goal of this development program, however, is to formulate a medication that provides the PD patient with an easier delivery system. We hypothesize that an orally available formulation will be easier to use, allow quicker control over predicted OFF periods, be more readily accessible to the patient when unpredicted OFFs occur during activities of daily living, and potentially be used by the milder PD patient when OFF episodes begin during the advancement of the disease.

8.4 Rationale

This study is designed to determine the appropriate starting dose for APL-130277 in patients with Parkinson's disease.
Results from this trial will allow APL-130277 to move in to an adequately powered, randomized, placebo controlled, registration trial as the first thin-strip delivery of apomorphine and will utilize a bilayer approach to overcome the historical short-comings of oral apomorphine applications.

9. OBJECTIVES

9.1 Clinical Objective

The primary objective of this study is to evaluate the efficacy, safety and tolerability of treatment with APL-130277 in 16 patients with Parkinson's Disease (PD).

9.2 Primary Variables

The primary variables will include:

a) Number of patients with resolution of an OFF episode to an ON state as assessed by the investigator at 15, 30, 45, 60 and 90 minutes after dosing. The investigators will use their clinical judgment to assess resolution of the OFF episode.
b) Time to ON from time of dosing
c) Duration of ON response
d) Tolerability: Percent of subjects that complete trial and experience an ON episode
e) Pharmacokinetic endpoints: PK profile, including: Cmax, Tmax, λz, t1/2, AUC, Kel.

9.3 Secondary Variables

Secondary endpoints include:

a) Safety and Tolerability endpoints: Evaluation of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including body temperature and weight), and adverse events.
b) Percent change in MDS-UPDRS Motor Score from pre-dose to 15, 30, 45, 60 and 90 minutes after dosing.

10. STUDY POPULATION

10.1 Selection of Study Population

The plan is for 16 patients to be enrolled into the study and proceed to the dosing day. To meet this goal, it is anticipated that up to 24 patients will be screened for study participation.

10.1.1 Inclusion Criteria

A subject will be eligible for study entry if all of the following inclusion criteria are met:

1. Male or female ≥18 years of age.
2. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria.
3. Receiving stable doses of L-dopa +/- other adjunctive PD therapy for at least 4 weeks before study participation.
4. At least one OFF episode per day and a total daily OFF time of ≥ 2 hours duration.
5. Experience predictable OFF episodes in the morning on awakening prior to receiving morning dose of levodopa.
6. Stage I to III on the Hoehn and Yahr scale in the "ON" state.
7. If female and of childbearing potential, must agree to use one of the following methods of birth control:
    - Oral contraceptive;
    - Contraceptive Patch;
    - Barrier (diaphragm, sponge or condom) plus spermicidal preparations;
    - Intrauterine contraceptive system;
    - Levonorgestrel implant;
    - Medroxyprogesterone acetate contraceptive injection;
    - Complete abstinence from sexual intercourse;
    - Hormonal vaginal contraceptive ring; or
    - Surgical sterilization or partner sterile (must have documented proof).
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.
9. Able to understand the consent form, and to provide written informed consent.

10.1.2 Exclusion Criteria

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Atypical or secondary parkinsonism.
2. Changes in L-dopa or other PD drug dosing regimens 4 weeks before the screening visit.
3. Past treatment with any form of apomorphine within 30 days of Dosing Day 1 (patients who stopped apomorphine for reasons other than lack of efficacy OR tolerability issues may be considered for the trial).
4. Female who is pregnant or lactating.
5. Contraindications to APOKYN or hypersensitive to apomorphine hydrochloride or any of the ingredients of APOKYN (notably sodium metabisulfite), or Tigan®.

6. Participation in any other clinical trial within 14 days of the screening visit.
7. Receipt of any investigational (i.e., unapproved) medication within 30 days of the screening visit.
8. Currently taking, or likely to need to take at any time during the course of the study, any 5HT3 antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron).
9. Currently taking dopamine antagonists or depleting drugs excluding anticholinergics and/or antihistamines with anticholinergic effects.
10. Drug or alcohol dependency in the past 6 months.
11. Clinically significant orthostatic hypotension.
12. Malignant melanoma or a history of previously treated malignant melanoma within 5 years.
13. Clinically significant medical surgical or laboratory abnormality in the judgment of the investigator.
14. Psychiatric disorder, including but not limited to dementia or any disorder that, in the opinion of the Investigator requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.
15. Dementia that precludes providing informed consent.
16. Potential for lack of compliance and follow-up in the judgment of the investigator.
17. Any other condition, current therapy, or prior therapy (within 30 days of the screening visit), which, in the opinion of the Investigator, would make the subject unsuitable for the study.
18. Previous neurosurgery for PD.
19. Donation of blood or plasma in the 30 days prior to dosing.
20. Presence of cankers or mouth sores.

11. TREATMENTS

11.1 Treatments to be Compared

Route: Sublingual

11.1.1 Drug Substance

The active ingredient is apomorphine hydrochloride hemihydrate ($C_{17}H_{17}NO_2$.HCl.½H_2O(salt)). Apomorphine is synthesized from morphine, but it is not a narcotic, nor is it a controlled substance. Apomorphine hydrochloride appears as minute, white or greyish-white glistening crystals or white powder. The R-enantiomer is used clinically.

The drug substance, apomorphine hydrochloride hemihydrate is manufactured by Sanofi-Aventis. Apomorphine hydrochloride is manufactured from morphine monohydrate in the presence of orthophosphoric acid, ethyl acetate and hydrochloric acid. Purification is performed in the presence of water, sodium chloride, sodium sulfite, ethyl acetate and silica gel.

A summary of physico-chemical data are provided below:

API Common name	Apomorphine Hydrochloride Hemihydrate
Production Site	Manufacture of Active Pharmaceutical Ingredient for Clinical Batches: Sanofi Aventis (Aramon Site) SANOFI CHIMIE Route d'Avignon 30390 Aramon France; Milling of active pharmaceutical ingredient for CTH-105 clinical supplies: The Jet Pulverizer Co. 1255 N. Church St. Moorestown, NJ 08057;
IUPAC nomenclature	4H-Dibenzo [de, g] quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl hydrochloride, hemihydrate
Synonyms, common names	Apomorphine hydrochloride, SR94013A, 6a,beta-aporphine-10,11-diol hydrochloride
CAS number	41372-20-7
Formula	$C_{17}H_{17}NO_2 \bullet HCl \bullet {}^1/_2H_2O$
Molecular weight	312.79 g/mol
Specific Rotation	-60.5° to -63.0°
pKa	pKa: 7.0, 8.9
pH	4.3
Water solubility	Sparingly soluble in water and alcohol; slightly

	soluble in chloroform

11.1.2 Drug Product (APL-130277 SL Film)

The product under development, APL-130277, is a soluble film strip for sublingual administration. APL-130277 is designed to deliver apomorphine systemically through absorption from the oral cavity, thus bypassing the extensive first pass metabolism associated with gastrointestinal absorption of the compound. The product is intended to be an alternative to the injectable form of apomorphine hydrochloride, which is marketed as Apokyn®.

APL-130277 is manufactured for clinical studies as a bilayer strip with one layer containing the active ingredient, apomorphine hydrochloride, and the other layer containing a buffer. Dosage units of 10, 15, 20, 25, and 30 mg are achieved from a single formulation by cutting different sized rectangular strips from sheets of bulk film:

Apomorphine Hydrochloride Loading (mg)	**Length (mm)**	**Width (mm)**	**Area (mm^2)**
10	22	8.8	193.6
15	22	13.2	290.4
20	22	17.6	387.2
25	22	22	484.0
30	22	26.4	580.8

The APL-130277 finished drug product will be manufactured at ARx, LLC facilities at: 400 Seaks Run Road Glen Rock, PA 17327, USA.

The formulations for each of the dosage strengths have exactly the same proportions of active pharmaceutical ingredient and inactive excipients.
The formulation consists of pharmaceutically acceptable cellulosic film formers along with glycerin as a plasticizer; and flavor, sweetener and color additives for patient acceptability. Other excipients include sodium hydroxide to modify pH and sodium metabisulfite as an antioxidant/preservative. The formulation also includes pyridoxine HCL as a buffer component. The excipients used in formulating APL-130277 sublingual film strips, are compendial (USP, NF or FCC) items and/or are Generally Recognized as Safe (GRAS) and/or have precedent for use in pharmaceutical products approved in the US.

11.1.3 Study Treatment

On Dosing Day 1, patients who are in an OFF state will be administered the starting dose of 10mg APL-130277. Treatment will proceed as per Section 12.1.2 Open Label Treatment Phase below.
APL-130277 is a near square bilayer film containing apomorphine hydrochloride. APL-130277 is intended for fast SL absorption for use in rescue therapy for acute intermittent OFF episodes experienced by Parkinson's patients. APL-130277 bilayer is composed of 2 layers laminated together: a first layer is composed of cellulose-ether based film,

containing drug substance, stabilizers and plasticizers; a second layer contains a pH-modifier (Pyridoxine Hydrochloride) contained within a similar cellulosic film base, flavor agents and a permeation enhancer.
The study staff will instruct the patient to consume a glass of water immediately prior to dosing. The study staff will confirm that the sublingual space is free of excess water before dosing.
Before dosing, the study staff will read out to patients:
"The product is a film. It will be placed beneath the tongue in the bottom of the mouth. After the dose is placed in the mouth, close your mouth naturally. Let your tongue take a natural position. Do not move the tongue around to try to taste the drug or change its position. Just let it slowly dissolve in place. It will dissolve in 1 to 2 minutes. During that time **try not to swallow saliva or the film**. When the film is dissolved, raise your hand to let the clinical staff know. We will ask that you open your mouth to show us."
The study staff will then place the film strip in the sublingual space of the patient with the drug layer facing toward the bottom of the tongue. Placement of the product can be performed with gloved hands or single-use, plastic disposable tweezers which will be supplied by the Sponsor (do not reuse or rinse, since any moisture on the tweezers can lead to dose sticking to the tweezers, leading to a problem with dosing).
The study staff will record: the time the film strip is placed under the tongue; the time the patient indicates the film strip is dissolved; the actual time the film strip is dissolved as verified by the study staff.

11.1.4 Packaging and Labeling

Each package of investigational drug product will be labeled with study-specific information meeting all the applicable regulatory requirements, including specifying the dose of apomorphine. Investigational drug product will be administered in the clinic.
Individual film strips of APL-130277 will be supplied packed into unit dose pouches. Each film strip is placed with the apomorphine drug layer facing down and to the side of the pouch containing the label, and the pyridoxine layer facing the side of the pouch that is marked with an "X" on the outside of the pouch.

11.1.5 Storage Conditions

The Investigator is responsible for ensuring the proper storage of the investigational drug product according to procedures agreed in advance. All study sites are required to keep investigational drug product in a locked cabinet or other secure storage contained with limited access to personnel.
Unit dose pouches of the investigational drug product must be stored at controlled room temperature: 68-77 °F (20-25°C), within a properly secured storage room and opened just before dosing. Temperature logs must be maintained for the storage room.
The Investigator must maintain accurate and adequate records including expiry dates, lot number, and quantities received individual usage, etc. The Investigator must also return unused supplies to the sponsor giving an account of usage in a trial whether or not the trial is completed or terminated. At the time of return to the Sponsor, the Investigator must verify that all unused or partially used drug supplies have been returned by the patient and that no remaining supplies are in the Investigator's possession. Certificates of delivery and returns must be signed and filed in the Study Site File.

11.2 Concomitant Therapy

All patients will be supplied with Tigan® which will be started on Day -3 and taken 300 mg tid up and to and including 1 day post the last dosing visit (Visit 5).
The investigator must record all medication used by the patient throughout the study in the EDC system.
This record will include the name of the medication, the total daily dose, route of administration, dates when drug was started and stopped, and the indication for drug usage.

11.2.1 Restrictions

1. Receipt of any investigational (i.e., unapproved) medication within 30 days of the screening visit or throughout the study.
2. Currently taking or have taken any form of apomorphine within 30 days of Dosing Day 1 (Visit 3).
3. Currently taking, or likely to need to take at any time during the course of the study, any 5HT3 antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron). Patients must wash out of these medications at least 14 days prior to the dosing visit (Visit 3).
4. Currently taking dopamine antagonists or depleting drugs excluding anticholinergics and/or antihistamines with anticholinergic effects. Patients must wash out of these medications at least 14 days prior to the dosing visit (Visit 3).

Additional study restrictions are provided in the table below.

Restriction	From	To
Use of drugs of abuse	6 months before first dose	After Final Visit
Use of any prescription or non-prescription medications unless discussed with Medical Monitor	14 days before first dose	After Final Visit
Strenuous exercise	3 days before first dose	After Final Visit
Donation of > 500 mL blood	30 days before first dose	After Final Visit
Donation of > 200 mL of plasma	30 days before first dose	After Final Visit

11.3 Treatment Compliance

All study medication will be administered by staff at the study sites.

12. INVESTIGATIONAL PLAN

12.1 Study Design

This is a multicentre, open-label Phase 2 study designed to determine the appropriate starting dose for APL-130277 in patients with Parkinson's disease. Following an up to 21-day screening phase, patients will return to the clinic at Day -1 to have pre-dosing assessments of safety completed, and to be instructed to take their last dose of levodopa no later than 10 PM that evening.
Patients will return the next morning to the clinic for assessment, and those who are in an OFF state will be administered the starting dose of 10mg APL-130277.
Following safety and efficacy assessments and failing a determination of resolution of the OFF episode by the Investigator or an incident of orthostatic hypotension, after 3 hours the patient will be administered the 15 mg film strip. If the patient does not respond in 90 minutes, the Investigator will administer levodopa.
Patients will be instructed to take their last dose of levodopa no later than 10 PM the evening before the next dosing visit.
Patients will return the next morning to the clinic for assessment, and those who are in an OFF state will be administered the next higher dose of APL-130277, or the dose at which an ON state was achieved at the previous visit. Following safety and efficacy assessments and failing a determination of resolution of the OFF episode by the Investigator or an incident of orthostatic hypotension, after 3 hours the patient will be administered the next higher film strip dose. If the patient does not respond to this dose in 90 minutes, the Investigator will administer levodopa.
Patients will be instructed to take their last dose of levodopa no later than 10 PM the evening before the next dosing visit. Patients who respond at the same dose of APL-130277 at the first two dosing visits will be considered complete in terms of dosing and proceed to the follow-up Visit.
Patients will return the next morning to the clinic for assessment, and those who are in an OFF state will be administered the next higher dose of APL-130277, or the dose at which an ON state was achieved at the previous visit. Following safety and efficacy assessments and failing a determination of resolution of the OFF episode by the Investigator or an incident of orthostatic hypotension, after 3 hours the patient will be administered the next higher dose of APL-130277. If the patient does not respond to this dose in 90 minutes, the Investigator will administer levodopa.
If the first dose administered at the visit is 30mg of APL-130277, the patient will proceed to the follow-up visit following a 90 minute assessment of response and resolution of the OFF episode with levodopa if required.
Dosing Days are not required to be sequential, but dosing must be completed within 7 days. Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day.
Patients will be seen for a follow-up visit on Day 7.

12.1.1 Screening Phase

Patients will be assessed over a 21 day period for study eligibility. During that time they will be seen at least twice in the clinic (Visits 1 and 2), be given Tigan® to start on Day -3

(300 mg tid orally) and will be seen at the second Visit (Visit 2) 1 day before dosing to have pre-dosing assessments of safety completed. Patients will be asked to take their last dose of Levodopa no later than 10 PM the evening of Day -1 and prepare to return to clinic the morning of Day 1 for dosing. At clinical sites where this is a possibility, patients, at their request and with their consent, may stay overnight in the clinic.

12.1.2 Open-label Treatment Phase

Patients will be seen on the morning of Dosing Day 1 (Visit 3), perform pre-dosing safety assessments and clinical assessments to determine their OFF status. Patients who are in an OFF state will be administered the starting dose of 10mg APL-130277. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from initial dosing and does not experience orthostatic hypotension as defined in Section 12.6, they will receive the 15mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

The patient will be asked to take their last dose of Levodopa no later than 10 PM the evening before the next dosing visit, and prepare to return the morning of Dosing Day 2 (Visit 4) for dosing. At clinical sites where this is a possibility, patients, at their request, and with their consent may stay overnight in the clinic.

Patients will be seen on the morning of Dosing Day 2 (Visit 4), perform pre-dosing safety assessments and clinical assessments to determine their OFF status.
Patients who are in an OFF state will be treated as follows:
If there was **no** response with either dose on Dosing Day 1 (Visit 3):

- Administer: 20mg APL-130277. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined in Section 12.6, they will receive the 25mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

If there was a response with either dose on Dosing Day 1 (Visit 3):

- Administer the dose that elicited an ON response on Dosing Day 1. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined in Section

12.6, they will receive the next higher dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

NOTE: Patients who responded to the same dose at Dosing Days 1 and 2 (Visits 3 and 4) will be considered complete from a dosing perspective, and proceed to Day 7 (Visit 6).

Patients who responded to a new dose at Dosing Day 2 (Visit 3), or who did not respond to either dose at Dosing Day 2 (Visit 3) will proceed to Dosing Day 3 (Visit 5).

The patient will be asked to take their last dose of Levodopa no later than 10 PM the evening before the next dosing visit, and prepare to return the morning of Dosing Day 3 (Visit 5) for dosing. At clinical sites where this is a possibility, patients, at their request, and with their consent, may stay overnight in the clinic.

Patients will be seen on the morning of Dosing Day 3 (Visit 5), perform pre-dosing safety assessments and clinical assessments to determine their OFF status.
Patients who are in an OFF state will be treated as follows:
If there was **no** response with either dose on Dosing Day 2:

- Administer the next higher dose of APL-130277. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined in Section 12.6, they will receive the next higher dose of APL-130277. If the first dose at this visit is 30mg APL-130277 the patient will be considered complete from a dosing perspective, receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state and proceed to Day 7 (Visit 6). For those patients dosed at a lower dose at this Visit than 30mg APL-130277, the same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

If there was a response with either dose on Dosing Day 2:

- Administer the dose that elicited a response on Dosing Day 2. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing and does not experience orthostatic hypotension as defined in Section 12.6, they will receive the next higher dose of APL-130277. If the first dose at this visit is 30mg APL-130277 the patient will be considered complete from a dosing perspective, receive

levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state and proceed to Day 7 (Visit 6). The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

Dosing Days are not required to be sequential, but dosing must be completed within 7 days. Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day.
Investigators will tailor instructions to patients outlined above based on their particular schedule of Dosing Days.
At all Dosing Days, if, in the opinion of the investigator, the patient does not move to an ON state 45 minutes after initial dosing, the patient should proceed to the next dose as per the protocol. Dose escalations following a questionable ON response should always be discussed with the medical monitor.

12.1.3 Follow-up
Patients will return to clinic on Day 7 for a full safety evaluation.

12.2 Study Procedures

As previously described, the study will be conducted across 4 visits and consist of three separate phases lasting up to 28 days, from start to finish. Specific study procedures and these phases will include:

1. Screening: Visits 1 and 2 (Days -21 to -1);
2. Active Period Visits:
   - Visit 3 (Dosing; Day 1);
   - Visit 4 (Dosing; Day 2);
   - Visit 5 (Dosing; Day 3);
3. Follow-Up: Visit 6 (Day 7).

Study procedures across each of these 3 phases are detailed below.

12.3 Screening: Visit 1 (Days -21 to -2)

Subjects must sign an ICF before any screening-related procedures are performed. Screening assessments must be performed within 21 days before the dosing Day (Visit 3, Day1). The assessments may be completed across several sub-visits during this period. The following specific study activities and procedures will be completed during this period:

- Review the study and obtain written informed consent. Subjects may review the consent and return it at a later date, at which time the screening visit will take place.
- Review inclusion/exclusion criteria.

- Record demographics and detailed medical history, including review of medications taken within 30 days prior to screening, Parkinson's disease, drug, alcohol and substance abuse history.
- Perform a complete physical examination (excluding genitourinary examination) with review of body systems.
- Measure height and weight and calculate BMI.
- Record vital signs (blood pressure, heart rate, respiratory rate, and body temperature) after the subject has been in a sitting position for 5 minutes.
- Perform a 12-lead ECG (Triplicate).
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, and urinalysis).
- Administer Hoehn and Yahr scale
- Administer Part III (Motor Function) of the MDS-UPDRS
- Dispense Tigan® (300 mg tid orally) and remind the subjects that they are to start this on Day -3.
- Schedule Visit 2.

12.4 Telephone Contact: T1 (Day -4)

Patients will be called on Day -4 to remind them to start their Tigan® (300 mg tid orally) on Day -3.

12.5 Screening: Visit 2 (Day -1) Baseline Day

Subjects will be asked to return to the study site on Day -1. The following procedures will take place:

- Reconfirmation of consent.
- Reconfirm use of anti-nausea medication since Day -3.
- Inclusion and exclusion / Restriction criteria assessed.
- Administer Part III (Motor Function) of the MDS-UPDRS
- Assessments of AEs since last visit.
- Measure Weight.
- Test strip application will proceed with all patients in preparation for dosing strip.
- Instruct the patient to take their last dose of levodopa that evening
- Instruct the patient on study restrictions

The Investigator will review all information obtained from the screening procedures. If the subject is not eligible, the subject will be a screening failure and will not attend any other visits. Subjects who fulfill all entry criteria will be found eligible to participate in the trial and an appointment for Visit 3 the next day will be made.

12.6 Active Period: Visit 3 Dosing Day 1

Subjects will be asked to return to the study site the next morning. The Investigator will review all the safety information collected to date and evaluate the patient's eligibility. Those patients considered eligible will continue at the Visit, and the following procedures will take place:

- Reconfirmation of consent.
- Reconfirm use of Tigan® (300 mg tid orally) since Day -3. Subjects may be excluded if medication was not taken appropriately. Dose given in clinic on Day 1
- Inclusion and exclusion and restriction criteria assessed.
- Assessments of AEs since last visit.
- Measure weight.
- Perform clinical confirmation of OFF prior to dosing; if the patient is not in the OFF state within 90 minutes, the patients should be rescheduled, and Investigators will tailor instructions to patients based on their particular schedule of Dosing Days.
- Vital signs (BP, HR, RR and Temp) at t=0 (just prior to dosing) and at t =0.25, 0.5, 0.75, 1.0, 1.5, hrs after each dose administered. Blood pressure is to be performed sitting and standing (measured within 3 minutes of standing), and sites are to carefully monitor patient for signs of orthostatic hypotension and stop dosing if orthostatic hypotension is experienced (protocol definition further down in this list)
- Perform a standard 12-lead ECG (Single) at t=0 (just prior to dosing) and at t =0.5, hrs after each dose administered
- Administer Part III (Motor Function) of the MDS-UPDRS at t = 0 (just prior to dosing), and at t=0.25, 0.5, 0.75, 1.0 and 1.5 hrs after each dose administered
- Patient is to consume a glass of water immediately prior to dosing.*
- Administer APL-130277 dosing strip* – starting at a dose of 10mg if patient in an OFF state
- Perform clinical confirmation of OFF or ON at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs after each dose administered
- Collect blood samples for PK at t = 0 (just prior to dosing) and at t = 10, 20, 30, 45, 60 and 90 minutes after each dose administered (at select sites only)
- If the patient does not move to an ON state within 3 hours from initial dosing and does not experience orthostatic hypotension as defined below, they will receive the 15mg dose of APL-130277*. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state, the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.
    - orthostatic hypotension, is defined as:
        - a decrease in systolic pressure < 90mmHg AND a decrease of >25% from Visit 3 pre-dose reading levels and/or
        - a diastolic pressure < 45mmHg AND a decrease of >25% from Visit 3 pre-dosing reading levels
- Conduct Abbreviated physical examination at the end of the Visit

The patient will be asked to take their last dose of Levodopa that evening, and prepare to return the morning of Dosing Day 2 (Visit 4) for dosing. At clinical sites where this is a possibility, patients, at their request, and with their consent, may stay overnight in the clinic.

The patient will be reminded to use Tigan® (300 mg tid orally).

The recommended sequence of assessments post-dosing at all dosing visits is as follows:

1. PK blood collection (for participating sites)
2. MDS-UPDRS motor function
3. Clinical confirmation of OFF/ON
4. Vital Signs
5. ECGs

12.7 Active Period: Visit 4 Dosing Day 2

The Investigator will review all the safety information collected to date and evaluate the patient's eligibility. Those patients considered eligible will continue at the Visit, and the following procedures will take place:

- Reconfirmation of consent.
- Reconfirm use of Tigan® (300 mg tid orally) since Dosing Day 1. Subjects may be excluded if medication was not taken appropriately. Dose given in clinic on Dosing Day 2
- Inclusion and exclusion and restriction criteria assessed.
- Assessments of AEs since last visit.
- Perform clinical confirmation of OFF prior to dosing; if the patient is not in the OFF state within 90 minutes, the patients should be rescheduled, and Investigators will tailor instructions to patients based on their particular schedule of Dosing Days.
- Patient is to consume a glass of water immediately prior to dosing.*
- Vital signs (BP, HR, RR and Temp) at t=0 (just prior to dosing) and at t =0.25, 0.5, 0.75, 1.0, 1.5, hrs after each dose administered. Blood pressure is to be performed sitting and standing (measured within 3 minutes of standing), and sites are to carefully monitor patient for signs of orthostatic hypotension and stop dosing if orthostatic hypotension is experienced (protocol definition further down in this list)
- Perform a standard 12-lead ECG (Single) at t=0 (just prior to dosing) and at t =0.5, hrs after each dose administered
- Administer Part III (Motor Function) of the MDS-UPDRS at t = 0 (just prior to dosing), and at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs after each dose administered

Patients who are in an OFF state will be treated as follows:
If there was **no** response with either dose on Dosing Day 1:

- Administer: 20mg APL-130277*. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined below, they will receive the 25mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard

dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

If there was a response with either dose on Dosing Day 1:

- Administer the dose that elicited a response on Dosing Day 1. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined below, they will receive the next higher dose of APL-130277*. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.
- Perform clinical confirmation of OFF or ON at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs after each dose administered
- Collect blood samples for PK at t = 0 (just prior to dosing) and at t = 10, 20, 30, 45, 60 and 90 minutes after each dose administered (at select sites only)
    - orthostatic hypotension, is defined as:
        - a decrease in systolic pressure < 90mmHg AND a decrease of >25% from this Visit pre-dose reading levels and/or
        - a diastolic pressure < 45mmHg AND a decrease of >25% from this Visit pre-dosing reading levels
- Conduct Abbreviated physical examination at the end of the Visit

NOTE: Patients who responded to the same dose at Visits 1 and 2 will be considered complete from a dosing perspective, and proceed to Day 7 (Visit 6).

Patients who responded to a new dose at Visit 2, or who did not respond to either dose at Visit 2 will proceed to Dosing Day 3 (Visit 5).

The patient will be asked to take their last dose of Levodopa that evening, and prepare to return the morning of Dosing Day 3 (Visit 5) for dosing. At clinical sites where this is a possibility, patients, at their request and with their consent, may stay overnight in the clinic.

The patient will be reminded to use Tigan® (300 mg tid orally).

12.8 Active Period: Visit 5 Dosing Day 3

The Investigator will review all the safety information collected to date and evaluate the patient's eligibility. Those patients considered eligible will continue at the Visit, and the following procedures will take place:

- Reconfirmation of consent.
- Reconfirm use of Tigan® (300 mg tid orally) since Dosing Day 2. Subjects may be excluded if medication was not taken appropriately. The patient will be dosed in clinic on Dosing Day 3.
- Inclusion and exclusion and restriction criteria assessed.
- Assessments of AEs since last visit.

- Perform clinical confirmation of OFF prior to dosing; if the patient is not in the OFF state within 90 minutes, the patients should be rescheduled, and Investigators will tailor instructions to patients based on their particular schedule of Dosing Days.
- Patient is to consume a glass of water immediately prior to dosing.*
- Vital signs (BP, HR, RR and Temp) at t=0 (just prior to dosing) and at t =0.25, 0.5, 0.75, 1.0, 1.5, hrs after each dose administered. Blood pressure is to be performed sitting and standing (measured within 3 minutes of standing), and sites are to carefully monitor patient for signs of orthostatic hypotension and stop dosing if orthostatic hypotension is experienced (protocol definition further down in this list)
- Perform a standard 12-lead ECG (Single) at t=0 (just prior to dosing) and at t =0.5, hrs after each dose administered
- Administer Part III (Motor Function) of the MDS-UPDRS at t = 0 (just prior to dosing), and at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs after each dose administered

Patients who are in an OFF state will be treated as follows:

If there was **no** response with either dose on Dosing Day 2:

- Administer the next higher dose of APL-130277*. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined below, they will receive the next higher dose of APL-130277*. If the first dose at this visit is 30mg APL-130277 the patient will be considered complete from a dosing perspective, receive levodopa at a dose considered appropriate by the investigator to achieve an ON state and proceed to Day 7 (Visit 6). For those patients dosed at a lower dose at this Visit than 30mg APL-130277, the same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

If there was a response with either dose on Dosing Day 2:

- Administer the dose of APL-130277* that elicited a response on Dosing Day 2. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing and does not experience orthostatic hypotension as defined in Section 12.6, they will receive the next higher dose of APL-130277*. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.
- Perform clinical confirmation of OFF or ON at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs after each dose administered
- Collect blood samples for PK at t = 0 (just prior to dosing) and at t = 10, 20, 30, 45, 60 and 90 minutes after each dose administered (at select sites only)
    - orthostatic hypotension, is defined as:

  - a decrease in systolic pressure < 90mmHg AND a decrease of >25% from this Visit pre-dose reading levels and/or
  - a diastolic pressure < 45mmHg AND a decrease of >25% from this Visit pre-dosing reading levels
- Conduct Abbreviated physical examination at the end of the Visit
- Instruct the patient on study restrictions, to continue dosing with Tigan® (300 mg tid orally) until the end of the following day and schedule the follow-up Visit (Day 7)

Dosing Days are not required to be sequential, but dosing must be completed within 7 days. Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day.
At all Dosing Days, if, in the opinion of the investigator, the patient does not move to an ON state 45 minutes after initial dosing, the patient should proceed to the next dose as per the protocol. Dose escalations following a questionable ON response should always be discussed with the medical monitor.

12.9 Visit 6: Follow-Up (Day 7)

The following will be completed at the outpatient visit on Day 7:
- Reconfirmation of subject's consent.
- A complete physical exam.
- Measurement of body weight.
- Assessment of vital signs
- A single 12-lead ECG with interpretation by the Investigator
- Clinical laboratory tests, including hematology, coagulation, blood chemistry and urinalysis.
- Assessment and documentation of all medications taken by the subject since the last assessment.
- Assessment and documentation of all AEs/SAEs since the subject's last visit to the CRU.
- Completion of the trial.

12.10 Subject Withdrawal from the Study

Subjects will be advised that they are free to withdraw from the study at any time, for any reason, and without prejudice. Every reasonable and appropriate effort should be made by the Investigator to keep patients in the study. However, subjects must be withdrawn from the study if the subject withdraws his or her consent to participate. The Investigator should record the reason for patient withdrawal.

The reason for discontinuation and the date of withdrawal from the study will be recorded in the EDC system.

Neither patients withdrawing from the study nor those removed by the Investigator or Cynapsus will be replaced. Patients who are withdrawn from this study may not re-enter the study at a later date. The patient number for a withdrawn subject will not be reassigned to another patient.

If a patient experiences severe vomiting and, in the opinion of the investigator, she/he cannot continue in the study, she/he may be discontinued from the trial. In this situation, all Day 7 trial related assessments should be completed.

The follow-up visit (Visit 6) will be conducted for every patient dosed with APL-130277, and the timing of the Visit can be as soon as the day immediately following last dosing.

12.11 Selection of the Doses Used in the Study

The dose selection used for the CTH-105 study will be 10mg, 15mg, 20mg, 25mg and 30 mg of APL-130277. The starting dose used in the CTH105 study is 10mg. This dose is selected based upon the PK profile observed in healthy volunteers in the CTH103 study. The dose was safe and well tolerated and produced a plasma concentration that was equivalent to a subcutaneous dose of apomorphine of between 1 and 2mg. In addition, a mean threshold plasma concentration of 3ng/ml (a dose where patients with Parkinson's disease see the onset of efficacy regarding the elimination of OFF) is achieved with this dose in the majority of subjects tested by about 14 minutes.
An escalation of doses in the clinic (based on achieving efficacy) to 15mg, 20mg, 25mg and 30mg results in exposures that are within the range used by s.c. apomorphine (2mg-5mg). Doses up to 25mg, have been tested in healthy volunteers. Due to toxicity with the comparator, doses of 30mg were not evaluated in healthy volunteers, however, based upon the dose proportional response seen with doses between 10mg and 25mg, it is anticipated that a dose of 30mg will achieve a plasma concentration equivalent to a dose between 4mg and 5mg of s.c. apomorphine (right around the median dose seen in patients using s.c. apomorphine as a rescue therapy presently).
Safety will be continually monitored as patients are titrated upwards as this will occur in the clinic under the supervision of the investigator and/or his/her staff.

13. STUDY PROCEDURES

13.1 Medical History

A complete medical history by body system will be performed on all patients at the screening visit (Visit 1). All active and resolved historical disorders will be recorded on the case report form. Current prescription and non-prescription medications will be recorded.

13.2 Physical Examination

A complete, head-to-toe physical examination (excluding genitourinary examination) will be completed on all patients at the screening visit (Visit 1) and follow-up (Visit 6) and will include the following assessments: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including mouth; musculoskeletal system; central and peripheral nervous system; and skin.
An abbreviated exam will be repeated before dosing and at t=1.5 hours post-dose at Visits 3-5 (head-eyes-ears-nose and throat, heart, lungs, abdomen and skin). All abnormal findings at baseline will be recorded on the Medical History/Concomitant Diagnoses page in the EDC system. New abnormal findings or worsening of baseline conditions detected at follow-up physical examinations will be recorded as adverse events in the EDC system.

13.3 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature, will be measured after the subject has been in a sitting position for 5 minutes. Vital signs will be assessed at Visit 1, at Visits 3-5 at t = 0 hrs (just prior to dosing) and at t =0.25, 0.5, 0.75, 1.0, 1.5, hrs post dosing and at Visit 6.

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Patients will be carefully monitored for signs of orthostatic hypotension and dosing will stop if protocol defined orthostatic hypotension results.

13.4 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed on all patients at the screening visit (Visit 1 – in triplicate) and performed (Single ECGs) at at t=0 (just prior to dosing) and at t =0.5, hrs after each dose administered at Visits 3 -5 and a single ECG performed at Visit 6. ECGs will be performed in a semi-recumbent position and after 5-minutes of rest. Recordings will include lead II as a rhythm strip and contain at least 5 QRS complexes. The interpretation of the ECG will be performed by the investigator or medically qualified designee. Investigators will note any clinically significant abnormalities.

The following ECG parameters will be reported in the eCRF for each ECG: heart rate, PR Interval, QRS Duration, RR Interval, QT Interval, QTc.
The purpose of the baseline ECG is to obtain information about the patient's baseline condition that may have not been elicited in obtaining the medical history. Therefore, any significant findings from this examination are recorded on the Medical History/Concomitant Diagnoses EDC screen. Clinically significant changes from baseline will be recorded as an Adverse Event.

13.5 Clinical Laboratory Tests

The following clinical laboratory test samples will be collected at Visits 1 and Visit 6:

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelet count (or estimate), WBC count including differential,
Serum Chemistry:	albumin, total bilirubin, total protein, alkaline phosphatase, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea, creatinine, glucose, sodium, potassium, uric acid, globulin, ,
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones

An explanation of the etiology of abnormal laboratory findings must be made on the laboratory report for any abnormalities for which an etiology is known.

13.5.1 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all personnel involved in the drawing of blood and the handling of specimens in both the clinic and laboratory settings.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study Laboratory Manual. It is the responsibility of the Investigator to ensure all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

Please see Laboratory Manual for details.

13.6 Adverse Events

Adverse events and use of concomitant medications will be assessed and recorded at every study visit from the time of signing of the ICF by the patient through Day 7 or earlier if warranted by a discontinuation. All adverse events must be recorded according to the procedures in Section 15.10 Adverse Events.

13.7 Hoehn and Yahr scale

The Hoehn and Yahr scale (5-6) will be administered at screening to verify patients are up to stage III motor impairment in the ON state. The Hoehn and Yahr scale administered for the study is the scale as it appears in the MDS-UPDRS (7).

13.8 Efficacy Assessments

13.8.1 Investigator confirmation of OFF or ON

Investigators will use their clinical judgment to assess the patient state of OFF or ON. The confirmation of OFF will be done prior to dosing and confirmation of OFF or ON will be done at 15, 30, 45, 60 and 90 minutes after each dose administered at Visits 3-5. Preferably, the same assessor will perform the assessments for each patient throughout the study.

13.8.2 MDS-UPDRS Motor Function

Investigators will administer the 14-item Motor Function section (section III) (7) of the MDS-UPDRS at Visits 1 and 2, and at t = 0 (just prior to dosing), 15, 30, 45, 60 and 90 minutes after each dose administered at Visits 3-5. Preferably, the same assessor will perform the assessments for each patient throughout the study.

13.8.3 Pharmacokinetic (PK) Parameters

Blood draws for APL-130277 PK analyses will occur at t = 0 (just prior to dosing) and at t = 10, 20, 30, 45, 60 and 90 minutes after each dose administered at Visits 3-5 at select sites only.

The following PK parameters will be derived from the serial assessments of plasma APL-130277 concentrations for each subject using standard noncompartmental methods:

$AUC_{0\text{-}24h}$ Area under the plasma concentration vs. time curve (hr·ng/mL) from dosing to the end of the 24-hour dosing interval, calculated using the linear trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids

$AUC_{0\text{-}4h}$ Area under the plasma concentration vs. time curve (hr·ng/mL) from dosing to 4 hr post-dosing, calculated using the linear trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids

$AUC_{0\text{-}\infty}$ Area under the plasma concentration vs. time curve (hr·ng/mL) from Hour 0.0 to infinity. $AUC_{0\text{-}\infty}$ is calculated as the sum of $AUC_{0\text{-}t}$ and $AUC_{t\text{-}\infty}$. The extrapolated $AUC_{t\text{-}\infty}$ is estimated as the ratio of the last measurable plasma concentration and the apparent terminal elimination rate constant (C_t/k_{el}). The percentage (%) of $AUC_{0\text{-}\infty}$ extrapolated will also be calculated.

C_{max} Maximum plasma concentration (ng/mL), observed by inspection of individual subject plots of plasma concentration versus time.
t_{max} Time (hr) from dosing to C_{max}, observed by inspection of individual subject plots of plasma concentration versus time
$t_{1/2}$ Apparent terminal elimination half-life (hr), as calculated by the following equation: $t_{1/2} = 0.693/\lambda_z$
MRT Mean residence time (hr) during one dosing interval calculated using the following equation: $MRT = AUMC_{0-\tau}/AUC_{0-\tau}$. $AUMC_{0-\tau}$ is the area under the first moment (time.plasma concentration vs. time) curve.
All derived PK parameters, and plasma APL-130277 concentrations at each scheduled assessment time point, will be summarized with descriptive statistics (arithmetic and geometric mean, standard deviation, coefficient of variation, median, range and number of observations). Graphical displays of individual subject mean plasma concentration versus time data will also be generated.
Pharmacokinetic analysis will be performed by Analytical Bio-Chemistry Laboratories, Inc. in Columbia, Missouri, and will take place following completion of the clinical phase of the trial, based on final quality controlled time points as recorded in the database. The final PK results will be included in the Summary Clinical Trial Report.
Pharmacokinetic sample preparation will be outlined in the Laboratory Manual.

14. STATISTICAL ANALYSES

This section presents a summary of the planned statistical analyses. A statistical analysis plan describing in detail the analyses to be conducted will be written prior to database lock. Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment. Statistics will be provided for all demographic, efficacy, pharmacokinetic and safety parameters listed below. Statistical tests will be 1-sided and differences will be considered statistically significant if $P \leq 0.025$, unless otherwise stated.
All details for analyses of efficacy and safety data will be presented in the SAP. Medical history and prior/concomitant medications will be coded using the World Health Organization drug dictionary (WHO-DRUG) and adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). Coding dictionary versions will be specified in the SAP.

14.1 Analysis Populations

Baseline demographic data for all subjects will be summarized with descriptive statistics (mean, standard deviation, median, range and number of observations) for quantitative parameters and by incidence rates for categorical findings.

14.1.1 Safety Population
The safety population is defined as all subjects who are enrolled into the study and have received at least 1 dose of the study drug.

14.1.2 Intention-to-Treat Population
The intention-to-treat (ITT) population is defined as all subjects who have received at least 1 dose of study drug and have at least one Investigator confirmation of OFF or ON.

14.1.3 Per-Protocol Population
The per-protocol (PP) population is defined as all subjects in the ITT population who complete the study and are deemed to be protocol-compliant. To be protocol-compliant, a subject will not have any major protocol violations during the entire study period.

14.1.4 PK Population
The PK population will be defined as those subjects that complete the PK blood sampling procedures as outlined in the protocol.

14.1.5 Handling of Missing and Incomplete Data

In general, missing or invalid data of efficacy assessments will be handled by individual scales or subscales on the basis of each individual assessment. Missing data for individual items will be assessed for each assessment of each scale and imputed with the mean score of the corresponding assessment and rounded up to the nearest integer if the number of items with missing data or invalid is less than or equal to 20% of total item number. Otherwise, the assessment score will be set to missing.

Handling of missing data will be described in detail in the SAP. For statistical analyses, missing data that result from either early study termination or unavailability will remain as missing for efficacy measures and safety measures, unless specified otherwise.

For the PK analyses, where individual data points were missing due to insufficient samples, dropouts, or other reasons, the missing datapoints will not be used in the analysis.

14.2 Primary Efficacy Analyses

The mean number of patients with resolution of an OFF episode to an ON state as assessed by the investigators at 15, 30, 45, 60 and 90 minutes after dosing will be compared across study treatment doses.
The time toON state from time of dosing in minutes will be calculated from timing noted by the investigators and recorded in the eCRF, and compared across study treatment doses.
The percent of subjects that complete trial and experience an ON episode as assessed by the investigators will be tabulated and compared across study treatment doses.
The duration of ON response in minutes will be calculated from the time noted by the investigators and recorded in the eCRF of an ON state to that of an OFF state on a per patient basis and compared across study treatment doses.

14.3 Secondary Efficacy Analysis

14.3.1 MDS-UPDRS Motor Score

The mean MDS-UPDRS Motor Score will be calculated across doses at pre-dose and 15, 30, 45, 60 and 90 minutes after dosing. The percent change in score from pre-dose to 15, 30, 45, 60 and 90 minutes after dosing will be calculated and compared across doses.

14.4 Pharmacokinetic Analysis

The following PK parameters will be derived from the serial assessments of plasma APL-130277 for each patient using standard noncompartmental methods.

$AUC_{0\text{-}24h}$ Area under the plasma concentration vs. time curve (hr·ng/mL) from dosing to the end of the 24-hour dosing interval, calculated using the linear

	trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids
$AUC_{0\text{-}4h}$	Area under the plasma concentration vs. time curve (hr·ng/mL) from dosing to 4 hr post-dosing, calculated using the linear trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids
$AUC_{0\text{-}\infty}$	Area under the plasma concentration vs. time curve (hr·ng/mL) from Hour 0.0 to infinity. $AUC_{0\text{-}\infty}$ is calculated as the sum of $AUC_{0\text{-}t}$ and $AUC_{t\text{-}\infty}$. The extrapolated $AUC_{t\text{-}\infty}$ is estimated as the ratio of the last measurable plasma concentration and the apparent terminal elimination rate constant (C_t/k_{el}). The percentage (%) of $AUC_{0\text{-}\infty}$ extrapolated will also be calculated.
C_{max}	Maximum plasma concentration (ng/mL), observed by inspection of individual subject plots of plasma concentration versus time.
t_{max}	Time (hr) from dosing to C_{max}, observed by inspection of individual subject plots of plasma concentration versus time
λ_z	Apparent terminal elimination rate constant (hr^{-1}), determined by log-linear regression of the plasma concentration versus time data that was judged to be in the log-linear elimination phase
$t_{1/2}$	Apparent terminal elimination half-life (hr), as calculated by the following equation: $t_{1/2} = 0.693/\lambda_z$
MRT	Mean residence time (hr) during one dosing interval calculated using the following equation: $MRT = AUMC_{0\text{-}\tau}/AUC_{0\text{-}\tau}$. $AUMC_{0\text{-}\tau}$ is the area under the first moment (time.plasma concentration vs. time) curve.

All derived PK parameters, and plasma APL-130277 concentrations at each scheduled assessment time point, will be summarized with descriptive statistics (arithmetic and geometric mean, standard deviation, coefficient of variation, median, range and number of observations). Graphical displays of individual subject mean plasma concentration versus time data will also be generated.

14.5 Safety Analysis

Safety variables include TEAEs, physical examination findings, vital signs and ECG measurements, and clinical laboratory test results. Physical examination findings related to oral examinations at dosing visits will be compared across study treatment doses.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with investigational drug and prior to 7 days after the end of treatment, or AEs starting prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The count and percentage of subjects with TEAEs will be displayed for each treatment group by body system and treatment arm. The preferred term will be based on the Medical Dictionary for Regulatory Activities (MedDRA). Tabulations of investigator judgments of severity and relationship to investigational drug will also be provided. Serious AEs (SAEs) will be summarized separately in a similar fashion. Subject listings of AEs causing discontinuation of investigational drug and SAEs will be produced.

The number and percentage of subjects with normal and abnormal ECG findings will be displayed for each treatment group at each time point. For ECG variables such as QTc, for vital signs variables, and for quantitative clinical laboratory tests, descriptive statistics including the count of abnormal measures will be presented. In addition mean, standard deviation, minimum, maximum, and median will be given for the values themselves as well as for change from baseline, by treatment group at each time point.

For qualitative clinical laboratory tests, the number and percentage of subjects with treatment-emergent abnormal findings in each category will be produced for each treatment group at each time point. For all clinical laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice-versa.

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group. Safety analyses will be conducted for the safety analysis population.

The number and percentage of subjects that complete the trial and experience an ON episode will be tabulated and displayed for each treatment group.

15. STUDY CONDUCT

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study site, review of protocol procedures with the Investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

15.1 Regulations and Guidelines

By signing this study protocol, the Investigator agrees to conduct this study in accordance with all laws, regulations and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 GCP and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the Principal Investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The Investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., subinvestigators and study coordinators) and their specific study related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, investigational drugs, and their specific duties within the context of the study. Investigators are responsible for providing Cynapsus with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by Cynapsus and the relevant governing authorities.

15.2 Ethics Approvals and Amendments

This study will be conducted in compliance with the Declaration of Helsinki and its amendments, the ICH Principles of Good Clinical Practice (GCP) (including archiving of essential study documents).
A properly constituted, valid Institutional Review Board (IRB) or Research Ethics Board (REB) must review and approve the protocol, the Investigator's informed consent document, and related patient information and recruitment materials before the start of the study. No study subjects will sign informed consent for the study until the study has received Ethics Committee approval. Protocol amendment procedures will not be implemented until Ethics Committee approval. If the protocol amendment substantially alters the study design or increases the potential risk or discomfort to the study subjects, written consent for continued participation in the study must be obtained from each subject.

15.3 Informed Consent

All the subjects will be given enough time to go over the purpose, procedures, potential risks and discomforts relating to this study. The subjects need to sign the informed consent form once they understand the procedure prior to the conduct of any study-related procedures, including screening.
The Investigator will verify the consent of each subject by signing and dating the relevant section of the source document. An original, signed copy of the consent form is given to each subject. Subjects will be able to contact the Investigator any time if they have queries concerning the study. They are aware that they are free to withdraw themselves from the study at any time without stating any reason. The original reference and signed consent forms will be filed in the study site file.

15.4 Study Initiation

Clinical site staff may not screen or enroll subjects into the study until receiving notification from Cynapsus or its designee that the study can be initiated at the clinical site. The clinical site will not be authorized for study initiation until:

- The clinical site has received the appropriate IRB/REB approval for the protocol and the IRB/REB-approved ICF
- The clinical site has a Clinical Trial Agreement in place

The clinical site personnel, including the Investigator, have participated in a study initiation meeting that includes specific training to help mitigate the placebo response.

15.5 Study Documentation

15.5.1 Investigator's Regulatory Documents

The regulatory documents listed below must be received from the Investigator and reviewed and approved by Cynapsus or its designee before the clinical site can initiate the study and before Cynapsus will authorize shipment of investigational drug to the clinical site. Copies of the Investigator's regulatory documents must be retained at the clinical site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the APL-130277 Investigator Brochure (IB), copies of regulatory references, copies of IRB/REB correspondence, and investigational drug accountability records should also be retained as part of the Investigator's regulatory documents. It is the Investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection. Cynapsus personnel will provide guidance as to what required documents are to be on-site at the initiation visit.

Documents Required for Regulatory Packet:

Confidentiality Agreement
Final Protocol
Protocol Amendments
Product insert for Apomorphine
Sub-I CV
Sub-I License
IRB Approvals

Protocol Signature Page	IRB Membership List / Assurance Statement
Protocol Amendments/ Signature Pages	Approved Informed Consent Template(s)
APL-130277 IB	Laboratory Certification
Signed Financial Disclosure	Laboratory Reference Ranges
PI CV	Laboratory Director CV
PI License	Laboratory Director License

15.5.2 Case Report Forms/EDC Modules

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain accurate CRFs/EDC modules and source documentation as part of the case histories for all subjects who sign an ICF.

CRFs/EDC modules are considered confidential documents and should be handled and stored accordingly. Cynapsus or its designee will provide the necessary training on the use of the specific EDC system used during the study to ensure that the information is captured accurately and appropriately.

In order to ensure data accuracy, EDC module data for individual subject visits should be completed as soon as possible following the visit. EDC data will be reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRA will verify data recorded with source documents.

All corrections or changes requested to the study data must be made as soon as possible by the study site, and verified by the Investigator. When all incorrect and/or inconsistent data has been accounted for, EDC data will be considered complete.

15.5.3 Source Documents

All information recorded in the in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include but are not limited to hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. If available, source documents for at least the 2 years prior to screening will be reviewed by the CRA to verify the subject's eligibility for the study.

During the study, select EDC data may be used as original data collection tools as long as a description of this documentation process is maintained in the Investigator's study files.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to Cynapsus or its designee. A paper copy of the laboratory results will be provided to the clinical site and must be retained with each subject's source data.

15.6 Data Quality Assurance

Cynapsus and its designees will perform quality control and assurance checks on all clinical studies that it sponsors.

15.6.1 Monitoring the Study

Clinical monitors will conduct site visits to the study facilities to monitor the study. The Investigator agrees to allow these monitors and other authorized Cynapsus personnel access. The clinical site will be monitored by Cynapsus and/or its designate to ensure compliance with the protocol, GCP, and applicable regulations and guidelines. As representatives of Cynapsus, CRAs are responsible for following the study protocol closely and notifying project management of any noted deviations. The assigned CRA(s) will visit the Investigator and clinical site at periodic intervals and maintain periodic communication. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. While on site, the CRA(s) will review regulatory documents, compare entries in the source documents, and review investigational drug accountability records. The CRA will ask for clarification and/or correction of any noted inconsistencies.

By signing the protocol, the Investigator agrees to meet with the CRA during clinical site visits, to ensure that study staff is available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area, and agrees to assist the monitors in their activities, if requested. The Investigator also agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

15.6.2 Routine Data Collection

EDC modules will be reviewed by the CRA during monitoring visits. The CRA will verify data with source documents. If the CRA's comparison of the original EDC module data with source documents reveals data discrepancies or omissions that require study staff to make corrections, the corrections will be made as outlined in the Study Monitoring Plan. After the EDC module data have been monitored and all corrections have been made, the Investigator must appropriately document within the data system his/her agreement with the data contained therein. If corrections are required subsequent to the Investigator's signature, the Investigator must document his/her agreement with the EDC module data to confirm the accuracy of the changed data. A copy of all EDC module data will be retained at the clinical site. If corrections are required after all data have been electronically transferred, the corrections must be made as instructed in site training.

15.6.3 Expedited Data Collection

Monitoring of selected EDC module data may occur following the EDC module completion. Any postsubmission/transfer corrections of EDC module data must be handled as instructed in clinical site training.

15.6.4 Data Management

Clinical site personnel will be responsible for providing resolutions to all data queries. The Investigator will be required to review and document electronic data to ensure the accuracy of the corrected and/or clarified data. This process must be handled as instructed in clinical site training.

15.7 Study Termination

The study may be terminated at Cynapsus' discretion at any time for any reason. If Cynapsus discovers conditions that warrant early termination of the study, the Investigator will be notified by Cynapsus or its designee. Examples of conditions that may warrant premature termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study; and
- The decision on the part of Cynapsus to suspend or discontinue testing, evaluation, or development of the investigational product.

15.8 Clinical Site Closure

On termination of the study, all screening and ongoing study related procedures conducted at the CRU will be closed. Cynapsus may terminate participation of the clinical site at any time. Examples of conditions that may warrant premature termination of a clinical site include, but are not limited to the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines, and
- Inadequate subject enrollment.
- Administrative reasons.

15.9 Data Monitoring Committee

The Medical Monitor and his team will act, in coordination with the Study Investigators, as the team monitoring the data from the study.

15.10 Adverse Event Reporting

15.10.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product. Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition.

15.10.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires in-subject hospitalization (being admitted) or prolongation of existing hospitalization
- Results in permanent (persistent) disability/incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the investigational drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.

A newly diagnosed pregnancy in the partner of a male subject who has received an investigational drug is not considered an SAE unless it is suspected that the investigational drug interacted with a contraceptive method and led to the pregnancy. A congenital anomaly in an infant born to a mother who was exposed to the investigational drug during pregnancy is an SAE.

15.10.3 Definition of Severity

The clinical "severity" of an AE will be classified as:

Mild:	Causes no limitation of usual activities
Moderate:	Causes some limitation of usual activities
Severe:	Prevents or severely limits usual activities

15.10.4 Definition of Start Date, Stop Date, and Duration

Start Date:	The date at which the AE is first noted
Stop Date:	The date at which the AE is known to be resolved. If it is not known to have stopped, then indicate "ongoing."
Duration:	A time in days, hours or minutes. (This is optional.)

15.10.5 Action(s) Taken

Action(s) taken may consist of:	
None:	No actions taken.
Discontinued Investigational Drug:	Investigational drug was permanently discontinued because of the AE.
Change Investigational Drug:	Investigational drug was given at a lower dose, at a longer interval between doses, or was temporarily withheld because of the AE.
Treatment:	Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure.
Others:	Other actions, such as an operative procedure, were required because of the AE.

15.10.6 Definition of Expectedness

An expected AE is an AE for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product (see Appendix A for s.c. apomorphine).

An unexpected AE is an AE for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and (b) hepatitis with a first occurrence of fulminate hepatitis.

15.10.7 Definition of Relationship to Investigational Drug(s)

The categories for classifying the Investigator's opinion regarding the relationship of an AE to investigational drug(s) are listed below:

Certain: An AE occurring in a plausible time relationship to investigational drug administration and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

Probable (likely): An AE with a reasonable time sequence to administration of the investigational drug and which is unlikely to be attributed to concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

Possible: An AE with a reasonable time sequence to administration of the investigational drug, but which could also be explained by

	concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Unlikely:	An AE, including laboratory test abnormality, with a temporal relationship to investigational drug administration that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Not related:	An AE with sufficient evidence to accept that there is no causal relationship to investigational drug administration (eg, no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven; etc.).
Unassessable (unclassifiable):	A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

15.10.8 Definition of Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Resolved
- Resolved with sequelae
- Ongoing
- Death
- Other
- Unknown

Death should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE.

15.10.9 Documentation of Adverse Events

The Investigator will monitor and/or ask about or evaluate AEs using non-leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date), or an indication of "ongoing"
- How long the AE persisted (optional)
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the investigational drug(s)

15.10.10 Follow-up of Subjects With an Adverse Event

Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication)

and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record.

15.10.11 Special Procedures for Managing Serious Adverse Events

If AEs occur in a subject which are not tolerable, or for which continued administration of investigational drug is not reasonable in view of the potential benefit to subject, the Investigator must decide whether to stop the study and/or treat the subject. In cases such as these, the Medical Monitor, Dr. Albert Agro should always be notified.

15.10.12 Notification of Sponsor of Serious Adverse Events

The Investigator must report all SAEs promptly to Cynapsus within 24 hours of first becoming aware of the event.

If an SAE occurs, the site should call Dr. Albert Agro at +1 647 529 5865 and confirm with email to: SAE@cynapsus.ca.

The Investigator must follow up the initial telephone notification by providing a written report by facsimile or mail describing the SAE to Cynapsus. This report may be accomplished by completing a Serious Adverse Event Form, which will be provided. At the time of first notification of an SAE, the study site should provide the following information to the Cynapsus contact person, if available:

- Subject's study number and initials
- Subject's date of birth
- Subject's gender
- Date of first dose of investigational drug(s)
- Date of last dose of investigational drug(s), if applicable
- AE term
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to investigational drug(s). ("Is there a reasonable possibility that the investigational drug caused the SAE? Yes or No?")
- Whether and when the Investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant information concerning the serious (or unexpected) AE should be provided in a written follow-up report.

The Investigator is required to comply with applicable regulations regarding the notification of his/her IRB or REB.

15.10.13 Notification of Cynapsus of Non-Serious Unexpected Adverse Events

All non-serious, unexpected AEs during the study, regardless of their relationship to the investigational drug(s), must also be reported to Cynapsus as soon as possible but no later than 24 hours after the event.

16. GENERAL CONSIDERATIONS

16.1 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Cynapsus. The protocol amendment must be signed by the Investigator and approved by the IRB or REB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

16.2 Use of Information and Publication

All information concerning APL-130277, Cynapsus' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Cynapsus to the Investigator and not previously published, is considered confidential and remains the sole property of Cynapsus. The EDC module printouts also remain the property of Cynapsus. The Investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Cynapsus in connection with the continued development of APL-130277 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Publication or other public presentation of APL-130277 data resulting from this study requires prior review and written approval of Cynapsus. Abstracts, manuscripts, and presentation materials should be provided to Cynapsus for review at least 30 days prior to the relevant submission deadline.

16.3 Records Retention

The Investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (1) 2 years after the last marketing authorization for the investigational drug has been approved or Cynapsus has discontinued its research with respect to such drug or (2) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify Cynapsus in writing of its intent to destroy all such material. Cynapsus shall have 30 days to respond to the Investigator's notice, and Cynapsus shall have a further opportunity to retain such materials at Cynapsus' expense.

16.4 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the study team has determined that specimens are no longer needed and the decision

has been made that there are no samples to be re-assayed. In addition, identifiable samples can be destroyed at any time at the request of the patient.

16.5 Subject Injury

In general, subject to specific provisions in the clinical study agreement (CSA), if a patient is injured as a direct result of a test article and the site, its staff and investigators have followed the protocol and all documentation supporting the proper running of the trial, Cynapsus will pay for reasonable and necessary medical treatment for the injury. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, Cynapsus shall comply with such laws or regulations. Where applicable, Cynapsus has taken specific national insurance.

17. REFERENCES

1. Schwab, R. S., Amador, L. V., & Lettvin, J. Y. (1951). Apomorphine in Parkinson's disease. *Transactions of the American Neurological Association, 56*, 251-253.
2. Cotzias, G., Papavasiliou, P., Fehling, C., Kaufman, B., &Mena, I. (1970). Similarities between neurologic effects of L-dopa and of apomorphine. *N Engl J Med* 2102 (1): 31–33.
3. Corsini, G. U., Zompo, M. D., Gessa, G. L., & Mangoni, A. (1979). Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. *The Lancet*, *313*(8123), 954-956.
4. Chaudhuri, K., & Clough, C. (1998). Subcutaneous apomorphine in Parkinson's disease. *BMJ*, *316*(7132), 641.
5. Hoehn, M. M., & Yahr, M. D. (1998). Parkinsonism: onset, progression, and mortality. *Neurology*, *50*(2), 318-318.
6. Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Counsell, C., ... & Seidl, L. (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations the Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Movement Disorders*, *19*(9), 1020-1028.
7. Goetz, C. G., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stebbins, G. T., ... & LaPelle, N. (2007). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Movement Disorders*, *22*(1), 41-47.
8. About BMI for adults. (2011, September 13). Center for Disease Control and Prevention. Retrieved from: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html#Interpreted
9. Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry*, *55*(3), 181-184.

18. APPENDICES

18.1 Appendix 1: APOKYN Prescribing Information

APOKYN
10 mg/mL For Subcutaneous Use Only Not for IV Use
Rx only

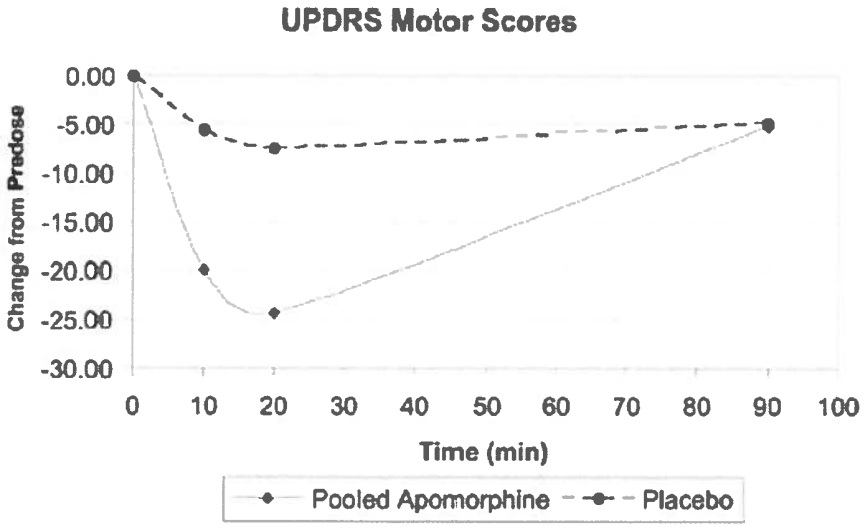
DESCRIPTION: APOKYN® (apomorphine hydrochloride, USP) is a non-ergoline dopamine agonist. Apomorphine hydrochloride is chemically designated as 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate with a molecular formula of C17H17NO2 • HCl • 1/2H2O. Its structural formula and molecular weight are:
Apomorphine hydrochloride appears as minute, white or grayish-white glistening crystals or as white powder that is soluble in water at 100°C.
APOKYN® 10 mg/mL is a clear, colorless, sterile solution for subcutaneous injection and is available in 3 mL cartridges. Each mL of solution contains 10 mg of apomorphine hydrochloride, USP as apomorphine hydrochloride hemihydrate and 1 mg of sodium metabisulfite, NF in water for injection, USP. In addition, each mL of solution may contain sodium hydroxide, NF and/or hydrochloric acid, NF to adjust the pH of the solution and 5 mg/mL of benzyl alcohol, NF as a preservative.
CLINICAL PHARMACOLOGY: Mechanism of Action: APOKYN is a non-ergoline dopamine agonist with high *in vitro* binding affinity for the dopamine D4 receptor (Ki = 4.4 nM), moderate affinity for the dopamine D2, D3, and D5 (Ki = 35-103, 26, and 15 nM, respectively), and adrenergic α1D, α2B, α2C (Ki = 65, 66, and 36 nM, respectively) receptors, and low affinity for the dopamine D1, serotonin 5HT1A, 5HT2A, 5HT2B, and 5HT2C (Ki = 370, 120, 120, 130, and 100 nM, respectively) receptors. Apomorphine exhibits no affinity for the adrenergic β1 and β2 or histamine H1 receptors (Ki > 10,000 nM).
The precise mechanism of action of APOKYN as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain. Apomorphine has been shown to improve motor function in an animal model of Parkinson's disease. In particular, apomorphine attenuates the motor deficits induced by lesions in the ascending nigrostriatal dopaminergic pathway with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates.
Pharmacokinetics: ***Absorption:*** Apomorphine hydrochloride is a lipophilic compound that is rapidly absorbed (time to peak concentration ranges from 10 to 60 minutes) following subcutaneous administration into the abdominal wall. After subcutaneous administration, apomorphine appears to have bioavailability equal to that of an intravenous administration. Apomorphine exhibits linear pharmacokinetics over a dose range of 2 to 10 mg following a single subcutaneous injection of apomorphine into the abdominal wall in patients with idiopathic Parkinson's disease.
Distribution: The plasma-to-whole blood apomorphine concentration ratio is equal to one. Mean (range) apparent volume of distribution was 2110 L (123 – 404 L). Maximum concentrations in cerebrospinal fluid (CSF) are less than 10% of maximum plasma concentrations and occur 10 to 20 minutes later.
Metabolism and Elimination: The mean apparent clearance (range) is 223 L/hr (125 – 401 L/hr) and the mean terminal elimination half-life is about 40 minutes (range about 30 to 60 minutes). The route of metabolism in humans is not known. Potential routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation. *In vitro,* apomorphine undergoes rapid autooxidation.
Special Populations: The clearance of apomorphine does not appear to be influenced by age,

gender, weight, duration of Parkinson's disease, levodopa dose or duration of therapy.
Hepatic Impairment: In a study comparing subjects with hepatic impairment (moderately impaired as determined by the Child-Pugh classification method) to healthy matched volunteers, the AUC0-∞ and Cmax values were increased by approximately 10% and 25%, respectively, following a single subcutaneous administration of apomorphine into the abdominal wall. Studies in subjects with severe hepatic impairment have not been conducted (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).
Renal Impairment: In a study comparing renally-impaired subjects (moderately impaired as determined by estimated creatinine clearance) to healthy matched volunteers, the AUC0-∞ and Cmax values were increased by approximately 16% and 50%, respectively, following a single subcutaneous administration of apomorphine into the abdominal wall. The mean time to peak concentrations and the mean terminal half-life of apomorphine were unaffected by the renal status of the individual. Studies in subjects with severe renal impairment have not been conducted. The starting dose for patients with mild or moderate renal impairment should be reduced (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).
Drug-Drug Interactions: ***Carbidopa/levodopa:*** Levodopa pharmacokinetics were unchanged when subcutaneous apomorphine and levodopa were co-administrated in patients. However, motor response differences were significant. The threshold levodopa concentration necessary for an improved motor response was reduced significantly, leading to an increased duration of effect without a change in the maximal response to levodopa therapy.
Other Drugs Eliminated Via Hepatic Metabolism: Based upon an *in vitro* study, cytochrome P450 enzymes play a minor role in the metabolism of apomorphine. *In vitro* studies have also demonstrated that drug interactions are unlikely due to apomorphine acting as a substrate, an inhibitor, or an inducer of cytochrome P450 enzymes.
COMT Interactions: A pharmacokinetic interaction of apomorphine with catechol-O-methyl transferase (COMT) inhibitors or drugs metabolized by this route is unlikely since apomorphine appears not to be metabolized by COMT.
Clinical Studies: The effectiveness of APOKYN in the acute symptomatic treatment of the recurring episodes of hypomobility, "OFF" episodes ("end-of-dose wearing OFF" and unpredictable "ON/OFF" episodes), associated with advanced Parkinson's disease was established in three randomized, controlled trials. On average, patients participating in these trials had Parkinson's disease for 11.3 years and were being treated with L-dopa and at least one other agent, usually an oral dopamine agonist. One of the three studies was conducted in patients who did not have prior exposure to apomorphine and two were conducted in patients with at least 3 months of apomorphine use immediately prior to study enrollment. Almost all patients without prior exposure to apomorphine began taking an antiemetic (trimethobenzamide) three days prior to starting apomorphine. After exposure to apomorphine, 50% of patients were able to discontinue use of a concomitant antiemetic, on average 2 months after initiating apomorphine.
Change in Part III (Motor Examination) of the Unified Parkinson's Disease Rating Scale (UPDRS) served as the primary outcome assessment measure in each study. Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, postural instability, etc.) in patients with Parkinson's disease.
The first trial used a parallel design, randomizing 29 patients with advanced Parkinson's disease to subcutaneous apomorphine or placebo in a 2:1 ratio. Patients had no prior exposure to apomorphine. In an office setting, hypomobility was allowed to occur by withholding the patients' Parkinson's disease medications overnight. The following morning, patients (in a hypomobile state) were started in a blinded fashion on study treatment (placebo or 2 mg of apomorphine) and redosed at increasing doses, after at least 2 hours, until a therapeutic response approximately equivalent to the individual patient's response to their usual dose of levodopa was observed (or until 10 mg apomorphine or placebo equivalent was given). At each redosing, study

drug was increased by 2 mg or 0.2 mL (to 4 mg, 6 mg, 10 mg, or 10 mg of apomorphine) or placebo equivalent. Of the 20 patients assigned to apomorphine, 110 achieved a therapeutic response at about 20 minutes that was approximately equivalent to the therapeutic response to a usual dose of levodopa. The average apomorphine dose was 5.4 mg (3 patients on 2 mg, 7 on 4 mg, 5 on 6 mg, 3 on 10 mg, and 2 on 10 mg). In contrast, of the 9 patients assigned to placebo, none reached such a therapeutic response. The mean changes-from-baseline for UPDRS Part III scores at the best dose were 23.9 and 0.1 for the apomorphine and placebo respectively ($p < 0.0001$).

The second trial used a crossover design, randomizing 17 patients who had been using apomorphine for at least 3 months. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received either a single dose of subcutaneous apomorphine (at their usual dose) or placebo. Their UPDRS Part III scores were then evaluated over time. The average dose of apomorphine was 4 mg (2 patients on 2 mg, 9 on 3 mg, 2 on 4 mg, and 1 each on4.5 mg, 5 mg, 10 mg, and 10 mg). On average, the mean changes-from-baseline UPDRS Part III scores at 20 minutes were 20.0 and 3.0 points for the apomorphine and placebo groups respectively ($p < 0.0001$).

The third trial used a parallel design, randomizing 62 patients who had been using apomorphine for at least 3 months. Patients were randomized in a 2:1 (active:placebo) ratio to one of four groups and were dosed once. The groups were: apomorphine at the usual dose, placebo at a volume matching the usual apomorphine dose, apomorphine at the usual dose + 2 mg (0.2 mL), or placebo at a volume matching the usual apomorphine dose + 0.2 mL. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received the randomized treatment. The mean changes-from-baseline for UPDRS Part III scores at 20 minutes post dosing were 24.2 and 7.4 points for the pooled apomorphine groups and the pooled placebo groups, respectively ($p < 0.0001$). The figure below describes the mean change in UPDRS Motor Scores over time after pooled apomorphine and pooled placebo administration.



In this third trial, comparing patients randomized to apomorphine at the usual dose (mean dose about 4.5 mg) and patients randomized to apomorphine + 2 mg (mean dose about 6 mg), the mean changes-from-baseline for UPDRS Part III scores at 20 minutes post dosing were 24 and

25, respectively. This suggests that patients chronically treated at a dose of 4 mg might derive little additional benefit from a dose increment of 2 mg. There was an increased incidence of adverse events in patients randomized to apomorphine + 2 mg.
INDICATIONS AND USAGE: APOKYN (apomorphine hydrochloride injection) is indicated for the acute, intermittent treatment of hypomobility, "OFF" episodes ("end-of-dose wearing off" and unpredictable "ON/OFF" episodes) associated with advanced Parkinson's disease. APOKYN has been studied as an adjunct to other medications (see CLINICAL PHARMACOLOGY: Clinical Studies).

CONTRAINDICATIONS:
Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with drugs of the 5HT3 antagonist class (including, for example, ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated.

APOKYN is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients (notably sodium metabisulfite).

WARNINGS:
Avoid Intravenous Administration: Serious adverse events (such as intravenous crystallization of apomorphine, leading to thrombus formation and pulmonary embolism) have followed the intravenous administration of apomorphine. Consequently, apomorphine should not be administered intravenously.

General: The significant adverse events described below have been reported in association with the use of subcutaneous apomorphine, but almost all of them occurred during open-label, uncontrolled studies. In the development program, the controlled trial data involved relatively few patients, and examined primarily the effects of single doses. Because the background rate of many of these events in a population of patients with advanced Parkinson's disease is unknown, it is difficult to assess the role of apomorphine in their causation.

Nausea and Vomiting: At the recommended doses of apomorphine, severe nausea and vomiting can be expected. Because of this, in domestic clinical studies, 910% of all patients were treated with the antiemetic trimethobenzamide for three days prior to beginning apomorphine and were then encouraged to continue trimethobenzamide for at least 6 weeks. Among 522 patients treated, 262 (50%) discontinued trimethobenzamide while continuing apomorphine. The average time to discontinuation of trimethobenzamide was about 2 months (range: 1 day to 33 months). For the 262 patients who discontinued trimethobenzamide, 249 patients continued apomorphine without trimethobenzamide for a duration of follow-up that averaged 1 year (range: 0-3 years). Even with the use of trimethobenzamide in clinical trials, 31% of the patients experienced nausea and 11% of the patients experienced vomiting. In clinical trials, 3% of the patients discontinued apomorphine due to nausea and 2% discontinued due to vomiting.
In the domestic development of apomorphine, there was no experience with antiemetics other than trimethobenzamide. Some antiemetics with anti-dopaminergic actions have the potential to worsen the clinical state of patients with Parkinson's disease and should be avoided.

Syncope: In clinical studies, about 2% of patients experienced syncope.
QT Prolongation and Potential for Proarrhythmic Effects: In a study in which patients received increasing single doses of apomorphine from 2 to 10 mg (if tolerated) as well as placebo,

the mean difference in QTc between apomorphine and placebo, as measured by Holter monitor, was 0 msec at 4 mg, 1 msec at 6 mg, and 7 msec at 10mg. Too few patients received a 10 mg dose to be able to adequately characterize the change in QTc interval at that dose. In a controlled trial in which patients were administered placebo or a single dose of apomorphine (mean dose of 5.2 mg; range of 2-10 mg, with 30 of 35 patients receiving a dose of 6 mg or less), the mean difference between apomorphine and placebo in the change in QTc was about 3 msec at 20 and 90 minutes. In the entire database, 2 patients (one at 2 and 4mg, one at 4mg) exhibited large QTc increments (> 60 msecs from pre-dose) and had QTc intervals greater than 500 msecs acutely after dosing. Doses of 4mg or less thus are associated with minimal increases in QTc. Doses greater than 4mg do not provide additional clinical benefit and are not recommended. Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsades de pointes and with sudden unexplained death. The relationship of QT prolongation to torsades de pointes is clearest for larger increases (20 msec and greater), but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, bradycardia, concomitant use of other drugs that prolong the QTc interval, or genetic predisposition (e.g., congenital prolongation of the QT interval). Although torsades de pointes has not been observed in association with the use of apomorphine at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. Palpitations and syncope may signal the occurrence of an episode of torsades de pointes. Caution is recommended when administering apomorphine to patients with the risk factors described above.

Symptomatic Hypotension: Dopamine agonists may cause orthostatic hypotension at any time, especially during dose escalation. Parkinson's disease patients, in addition, may have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk.
Apomorphine causes dose-related decreases in systolic (SBP) and diastolic blood pressure (DBP). Dose-dependent mean decrements in SBP ranged from 5 mmHg after 2 mg to 16 mmHg after 10 mg. Dose-dependent mean decrements in DBP ranged from 3 mmHg after 2 mg to 10 mmHg after 10 mg. These changes were observed at 10 minutes, appeared to peak at about 20 minutes after dosing, and persisted up to at least 90 minutes post-dosing. Patients undergoing titration of apomorphine showed an increased incidence (from 4% pre-dose to 110% post-dose) of systolic orthostatic hypotension (≥ 20 mmHg decrease) when evaluated at various times after in-office dosing. A small number of patients developed severe systolic orthostatic hypotension (≥ 30 mmHg decrease and systolic BP ≤ 90 mmHg) after subcutaneous apomorphine injection.
In clinical trials of apomorphine in patients with advanced Parkinson's disease, 59 of 550 patients (11%) had orthostatic hypotension, hypotension, and/or syncope. These events were considered serious in 4 patients (< 1%) and resulted in withdrawal of apomorphine in 10 patients (2%). These events occurred both with initial dosing and during long-term treatment. Whether or not hypotension contributed to other significant adverse events seen (e.g., falls), is unknown.
The effects of apomorphine on blood pressure may be increased by the concomitant use of alcohol, antihypertensive medications, and vasodilators (especially nitrates). Alcohol should be avoided when using APOKYN and extra caution should be exercised if APOKYN must be administered with concomitant antihypertensive medications and/or vasodilators (see PRECAUTIONS: Drug Interactions and Information for Patients). **Falls:** Patients with Parkinson's disease (PD) are at risk of falling due to the underlying postural instability and concomitant autonomic instability seen in some patients with PD, and from syncope caused by the blood pressure lowering effects of the drugs used to treat PD. Subcutaneous apomorphine

might increase the risk of falling by simultaneously lowering blood pressure and altering mobility (see WARNINGS: Symptomatic Hypotension; PRECAUTIONS: Dyskinesias).
In clinical trials, 30% of patients had events that could reasonably be considered falls and about 5% of patients had falls that were considered serious. Because these data were obtained in open, uncontrolled studies, and given the unknown background rate of falls in a population of patients with advanced Parkinson's disease, it is impossible to definitively assess the contribution of apomorphine to these events.

Hallucinations / Psychotic-Like Behavior: During clinical development, hallucinations were reported by 14% of the patients. In one randomized, double-blind, placebo-controlled study, hallucinations or confusion occurred in 10 % of patients treated with APOKYN and 0 % of patients treated with placebo. Hallucinations resulted in discontinuation of apomorphine in 1% of patients.
Post marketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior after starting or increasing the dose of APOKYN. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations, including paranoid ideation, delusions, hallucinations, confusion, disorientation, aggressive behavior, agitation, and delirium.
Patients with a major psychotic disorder should ordinarily not be treated with APOKYN because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of APOKYN. (see PRECAUTIONS: Drug Interactions: *Dopamine Antagonists*)

Falling Asleep During Activities of Daily Living: There have been reports in the literature of patients treated with apomorphine subcutaneous injections who suddenly fell asleep without prior warning of sleepiness while engaged in activities of daily living. It is clear that somnolence is commonly associated with APOKYN and many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence even if patients do not give such a history. Prescribers should therefore continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.
Before initiating treatment with APOKYN, patients should be advised of the possibility that they may develop drowsiness and specifically asked about factors that could increase the risk with APOKYN, such as concomitant sedating medications and the presence of sleep disorders. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), APOKYN should ordinarily be discontinued. If a decision is made to continue APOKYN, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to determine whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Coronary Events: During clinical development, 4% of patients treated with apomorphine experienced angina, myocardial infarction, cardiac arrest and/or sudden death; some cases of angina and myocardial infarction occurred in close proximity to apomorphine dosing (within 2 hours), while other cases of cardiac arrest and sudden death were observed at times unrelated to dosing. Apomorphine has been shown to reduce resting systolic and diastolic blood pressure

and, as such, it has the potential to exacerbate coronary (and cerebral) ischemia. Extra caution should be used in prescribing apomorphine for patients with known cardiovascular and cerebrovascular disease. If patients develop signs and symptoms of coronary or cerebral ischemia, the continued use of apomorphine should be carefully re-evaluated.

Contains Sulfite: APOKYN contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Injection Site Reactions: Among the 550 patients treated with apomorphine subcutaneous injections during development, 26% of patients complained of injection site reactions, including bruising (16%), granuloma (4%), and pruritus (2%). There was a limited experience (both for overall numbers of patients as well as the total number of injections per patient) with apomorphine injections in controlled trials. In this limited controlled experience, the number of injection site reactions reported by patients receiving apomorphine was similar to that reported by patients receiving placebo.

Potential for Abuse: There are rare reports of apomorphine abuse by patients with Parkinson's disease in other countries. These cases are characterized by increasingly frequent dosing leading to hallucinations, dyskinesia, and abnormal behavior. Psychosexual stimulation with increased libido is believed to underlie these cases. Prescribers should be vigilant for evidence that patients are abusing apomorphine, such as use out of proportion to motor signs (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS: Dyskinesias: Apomorphine may cause dyskinesia or exacerbate pre-existing dyskinesia. During clinical development, dyskinesia or worsening of dyskinesia was reported in 24% of patients. Overall, 2% of patients withdrew from studies due to dyskinesias.

Events Reported with Dopaminergic Therapy: Although the events enumerated below have not been reported in association with the use of apomorphine, they are associated with the use of other dopaminergic drugs.

Withdrawal-emergent Hyperpyrexia and Confusion: Although not reported with apomorphine, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

Fibrotic Complications: Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.
Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using APOKYN for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Priapism: Apomorphine may cause prolonged painful erections in some patients. During clinical development, painful erections were reported by 3 of 361 males (< 1%), and one patient withdrew from apomorphine therapy because of priapism. Although no patients in the clinical development program required surgical intervention, severe priapism may require surgical intervention.

Hepatic Impairment: Caution should be exercised when administrating apomorphine to patients with mild and moderate hepatic impairment due to the increased Cmax and AUC in these patients. Studies of subjects with severe hepatic impairment have not been conducted (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Renal Impairment: The starting dose should be reduced to 1 mg when administrating apomorphine to patients with mild or moderate renal impairment because the Cmax and AUC are increased in these patients. Studies in subjects with severe renal impairment have not been conducted (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Retinal Pathology in Albino Rats: Retinal degeneration has been observed in albino rats treated with dopamine agonists for prolonged periods (generally during 2-year carcinogenicity studies). This lesion has also been observed when albino rats were exposed to these agents for shorter periods under higher intensity light exposures. Similar changes have not been observed in 2-year carcinogenicity studies in albino mice or in rats or monkeys treated for 1 year. APOKYN has not been tested in carcinogenicity studies, but based on its mechanism of action it would be expected to cause similar toxicity. The significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved. **Information for Patients:** APOKYN is intended only for subcutaneous injection and must not be given intravenously. Patients and caregivers should be urged to read the attached Patient Package Insert and Directions for Use for the dosing pen. Patients should be instructed to use APOKYN only as prescribed. Patients and/or caregivers who are advised to administer APOKYN in medically unsupervised situations should receive instruction on the proper use of the product from the physician or other suitably qualified health care professional and then observed during the initial dosing.

In particular, patients and caregivers must receive detailed instruction in the use of the dosing pen, with particular attention paid to two issues: 1) Patients need to be aware that the drug is dosed in milliliters, not milligrams. Patients should be particularly cautioned that a dose of 1 mg is represented on the dosing pen as 0.1 mL, and not as 1.0 (the latter representing a dose of 10 mg). It is critical that patients and caregivers be made to understand this distinction to prevent potentially life-threatening overdose if a dose of 1 mg is prescribed. 2) Patients and caregivers must be informed that it is possible to dial in their usual dose of apomorphine even though the cartridge may contain less than that amount of drug. In this case, they will receive only a partial dose with the injection, and the amount left to inject will appear in the dosing window. To complete the correct dose, patients/caregivers will need to "re-arm" the device and dial in the correct amount of the remaining dose. If at all possible, this situation should be avoided, and patients and caregivers should be alerted to the fact that there may be insufficient drug left in the cartridge to deliver a complete dose (for example, patients and caregivers should be urged

to keep records of how many doses they have delivered for each cartridge, so that they can replace any cartridge that has an inadequate amount of drug remaining).

Patients should be instructed to rotate the injection site and to observe proper aseptic technique.
Patients should be informed that hallucinations or other manifestations of psychotic-like behavior can occur. Patients should also be advised that, if they have a major psychotic disorder, that APOKYN should not ordinarily be used because of the risk of exacerbating the psychosis. Patients with a major psychotic disorder should also be aware that many treatments for psychosis may decrease the effectiveness of APOKYN. (see PRECAUTIONS: Drug Interactions: *Dopamine Antagonists*).
Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after months of treatment). Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been sitting or lying for prolonged periods, and especially at the initiation of treatment with APOKYN. Alcohol, antihypertensive medications, and vasodilating medications may potentiate the hypotensive effect of apomorphine (see WARNINGS: Symptomatic Hypotension; PRECAUTIONS: Drug Interactions).
Patients should be alerted to the potential sedating effects of APOKYN, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with APOKYN to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with **APOKYN.**
Because apomorphine has not been evaluated for effects on reproduction and embryo-fetal development, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant (see PRECAUTIONS: Pregnancy).
Because of the possibility that apomorphine may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed.
There have been reports of patients experiencing intense urges to gamble, increased sexual urges, other intense urges and the inability to control these urges while taking one or more of the medications that increases central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including APOKYN. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with APOKYN. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking APOKYN. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking APOKYN.
Rare cases of abuse (use of apomorphine significantly in excess of prescribed frequency) have been reported. Apomorphine abuse may be associated with inappropriate sexual behavior.

Drug Interactions:

5HT3 Antagonists: Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with drugs of the 5HT3 antagonist class (including, for example, ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated (see CONTRAINDICATIONS).

Antihypertensive Medications and Vasodilators: The following adverse events were experienced more commonly in patients receiving concomitant antihypertensive medications or vasodilators (n = 94) compared to patients not receiving these concomitant drugs (n = 456): hypotension 10% vs 4%, myocardial infarction 3% vs 1%, serious pneumonia 5% vs 3%, serious falls 9% vs 3%, and bone and joint injuries 6% vs 2%. The mechanism underlying many of these events is unknown, but may represent increased hypotension (see WARNINGS: Symptomatic Hypotension).

Dopamine Antagonists: Since apomorphine is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of APOKYN. Patients with major psychotic disorders, treated with neuroleptics, should be treated with dopamine agonists only if the potential benefits outweigh the risks.

Drugs Prolonging the QT/QTc Interval: Caution should be exercised when prescribing apomorphine concomitantly with drugs that prolong the QT/QTc interval (see WARNINGS: QT Prolongation and Potential for Proarrhythmic Effects).

Drug/Laboratory Test Interactions: There are no known interactions between APOKYN and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been conducted with APOKYN. Apomorphine was mutagenic in the *in vitro* bacterial Ames test and the *in vitro* mammalian mouse lymphoma assay. Apomorphine was also clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes and the *in vitro* mouse lymphoma assay. Apomorphine was negative in the *in vivo* micronucleus assay in mice.
In a published fertility study in male rats, an adverse effect on fertility was observed at a dose of 2 mg/kg administered subcutaneously (0.6 times the MRHD in a mg/m2 basis). A significant decrease in testis weight was observed in a 39-week study in cynomolgus monkey at subcutaneous doses of 1.0 and 1.5 mg/kg (0.6 and 1 times the MRHD on a mg/m2 basis).

Pregnancy: Pregnancy Category C: Reproduction studies have not been conducted with apomorphine. It is also not known whether apomorphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Apomorphine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether apomorphine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from apomorphine, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of APOKYN in pediatric patients has not been established.

Geriatric Use: In the apomorphine clinical development program, there were 239 patients less than 65 years of age and 311 who were 65 years of age or older. Adverse events were about equally common in older and younger patients (90 vs 107%), but with older patients more likely to experience confusion and hallucinations. Serious adverse events (life-threatening events or events resulting in hospitalization and/or increased disability) were also more common in older patients (27 vs 17%), with older patients more likely to fall (experiencing bone and joint injuries), have cardiovascular events, develop respiratory disorders, and have gastrointestinal events. Older patients were more likely to discontinue apomorphine treatment as a result of adverse events (29 vs 21%).

ADVERSE REACTIONS Clinical Trial Experience Adverse Events Incidence in Controlled Clinical Studies: APOKYN® has been administered to 550 Parkinson's disease patients who were taking some form of L-Dopa along with other Parkinson's disease medications. Eighty-six percent of patients were taking a concomitant dopamine agonist. All patients had some degree of spontaneously occurring hypomobility ("OFF episodes") at baseline. Adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using MEDDRA dictionary terminology. The most common adverse events seen in controlled trials were yawning, dyskinesias, nausea and/or vomiting, somnolence, dizziness, rhinorrhea, hallucinations, edema, chest pain, increased sweating, flushing, and pallor.
The most extensive experience with apomorphine in randomized, controlled trials comes from a multicenter randomized placebo-controlled parallel group trial conducted in apomorphine-naïve PD patients treated for up to 4 weeks (Table 1). Individual apomorphine doses in this trial ranged from 2-10 mg, optimized to achieve control of symptoms comparable to each patient's response to his or her usual dose of L-dopa. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Table 1 Summary of Adverse Events Occurring in Two or More Patients

Adverse Event	APOMORPHINE		PLACEBO	
	n = 20		n = 9	
	N	%	N	%
Any Adverse Reaction	17	105	10	109
Yawning	10	40	0	0
Dyskinesias	7	35	1	11
Drowsiness or Somnolence	7	35	0	0
Nausea and/or Vomiting	6	30	1	11
Dizziness or Postural Hypotension	4	20	0	0
Rhinorrhea	4	20	0	0
Chest Pain/Pressure/Angina	3	15	1	11
Hallucination or Confusion	2	10	0	0
Edema/Swelling of Extremities	2	10	0	0

Other Adverse Events Observed During All Phase 2/3 Clinical Trials: APOKYN has been administered to 550 patients; 89% had at least one adverse event (AE). The most common AEs in addition to those in Table 1 (occurring in at least 5% of the patients and at least plausibly related to treatment) in descending order were injection site complaint, fall, arthralgia, insomnia, headache, depression, urinary tract infection, anxiety, congestive heart failure, limb pain, back pain, Parkinson's disease aggravated, pneumonia, confusion, sweating increased, dyspnea, fatigue, ecchymosis, constipation, diarrhea, weakness, and dehydration.

Post Marketing Experience:
In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of APOKYN® in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following psychiatric disorders were reported: impulse control symptoms, pathological gambling, and increased libido (including hypersexuality).

DRUG ABUSE AND DEPENDENCE: Potential for Abuse:
A rarely reported motivation for apomorphine abuse (escalation of dose beyond prescribed frequency) is the use of apomorphine to attempt to avoid all symptoms of all "OFF" events when "OFF" events occur frequently. A second, rarely reported, motivation for apomorphine abuse is a psychosexual reaction related to the stimulation of penile erection and increase in libido. Adverse events that have been reported in males with overuse include frequent penile erections, atypical sexual behavior, heightened libido, dyskinesias, agitation, confusion, and depression. No studies have been conducted to evaluate the potential for dependence when apomorphine is used as acute (rescue) treatment of "OFF" episodes in the patients with "ON/OFF" or "wearing-off" effects associated with late stage Parkinson's disease.

OVERDOSAGE: Intermittent Injection:
A report of an accidental overdose of 25 mg injected subcutaneously in a 62 year old man was published in Journal of Neurology, Neurosurgery, and Psychiatry (1990), Vol. 53, pp. 96-102. After 3 minutes, the patient felt nauseated and lost consciousness for 20 minutes. Afterwards, he was alert with a heart rate 40/minute and a supine blood pressure of 90/50. He recovered completely within an hour.

DOSAGE AND ADMINISTRATION: The prescribed dose of APOKYN should always be expressed in mL to avoid confusion and doses greater than 0.6 mL (6 mg) are not recommended. Patients and caregivers must receive detailed instructions in the preparation and injection of doses, with particular attention paid to the correct use of the dosing pen (see PRECAUTIONS: Information for Patients).
APOKYN is indicated for subcutaneous administration only. APOKYN should not be initiated without use of a concomitant antiemetic (see WARNINGS: Nausea and Vomiting). Most antiemetic experience is with trimethobenzamide and this should generally be used. Trimethobenzamide (300 mg tid orally) should be started 3 days prior to the initial dose of apomorphine and continued at least during the first two months of therapy.
Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with drugs of the 5HT3 antagonist class (including, for example, ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated (see CONTRAINDICATIONS).
The dose of APOKYN must be titrated on the basis of effectiveness and tolerance, starting at 0.2 mL (2 mg) and up to a maximum recommended dose of 0.6 mL (6 mg) as follows:

Patients in an "OFF" state should be given a 0.2 mL (2 mg) test dose in a setting where blood pressure can be closely monitored by medical personnel. Both supine and standing blood pressure should be checked predose and at 20, 40, and 60 minutes post dose. Patients who develop clinically significant orthostatic hypotension in response to this test dose of apomorphine should not be considered candidates for treatment with APOKYN. If the patient tolerates the 0.2 mL (2 mg) dose, and responds, the starting dose should be0.2 mL (2 mg) used on an as needed basis to treat existing "OFF" episodes. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis.

Beyond this, the general principle guiding dosing (described in detail below) is to determine a dose (0.3 mL or 0.4 mL) that the patient will tolerate as a test dose under monitored conditions, and then begin an outpatient dosing trial (periodically assessing both efficacy and tolerability) using a dose 0.1 mL (1 mg) lower than the tolerated test dose.

For patients who tolerate the test dose of 0.2 mL (2 mg) but achieve no response, a dose of 0.4 mL (4 mg) may be administered at the next observed "OFF" period, but no sooner than 2 hours after the initial test dose of 0.2 mL (2 mg). Both supine and standing blood pressure should be checked predose and at 20, 40, and 60 minutes post dose. If the patient tolerates a test dose of 0.4 mL (4 mg) the starting dose should be 0.3 mL (3 mg) used on an as needed basis to treat existing "OFF" episodes. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis. If a patient does not tolerate a test dose of 0.4 mL (4 mg), a test dose of 0.3 mL (3 mg) may be administered during a separate "OFF" period, no sooner than 2 hours after the test dose of 0.4 mL (4 mg). Both supine and standing blood pressure should be checked predose and at 20, 40, and 60 minutes post dose. If the patient tolerates the 0.3 mL (3 mg) test dose, the starting dose should be 0.2 mL (2 mg) used on an as needed basis to treat existing "OFF" episodes. If needed, and the 0.2 mL (2 mg) dose is tolerated, the dose can be increased to 0.3 mL (3 mg) after a few days. In such a patient, the dose should ordinarily not be increased to 0.4 mL (4 mg) on an outpatient basis.

Most patients studied in the apomorphine development program responded to 0.3 mL to 0.6 mL (3 mg to 6 mg). There is no evidence from controlled trials that doses greater than 0.6 mL (6 mg) give an increased effect and these doses are not recommended. The average frequency of dosing was 3 times per day in the development program, and there is limited experience with single doses greater than 0.6 mL (6 mg), dosing more than 5 times per day and with total daily doses greater than 2.0 mL (20 mg).

If a single dose of apomorphine is ineffective for a particular "OFF" period, a second dose should not be given for that "OFF" episode. The efficacy of a second dose for a single "OFF" episode has not been systematically studied and the safety of redosing has not been characterized.

Patients who have a significant interruption in therapy (more than a week) should be restarted on a 0.2 mL (2 mg) dose and gradually titrated to effect.

When dosing patients with mild and moderate hepatic impairment, caution should be exercised due to the increased Cmax and AUC in these patients (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

For patients with mild and moderate renal impairment, the testing dose and subsequently the starting dose should be reduced to 0.1 mL (1 mg) (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

18.2 Appendix 2: Calculation of Body Mass Index in Imperial Units (8)

Body Mass Index (BMI) is determined by weight and height according to the following equation; weight (lb) / [height (in)]^2 x 703

Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703.

. An online calculator can be found here (accessed: June 10, 2014):
http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html

Note: The latest version of the scale with instructions and scoring will be implemented in the study

18.3 Appendix 3: Movement Disorder Society Unified Parkinson's Disease Rating Scale - Motor Function (Section III):

III: MOTOR EXAMINATION

3.1 SPEECH
0: Normal: No speech problems.
1: Slight: Loss of modulation, diction or volume, but still all words easy to understand.
2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow.
3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood.
4: Severe: Most speech is difficult to understand or unintelligible

3.2 FACIAL EXPRESSION
0: Normal: Normal facial expression.
1: Slight: Minimal masked facies manifested only by decreased frequency of blinking.
2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.
3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest.
4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.

3.3 RIGIDITY
0: Normal: No rigidity.
1: Slight: Rigidity only detected with activation maneuver.
2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.
3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.
4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

3.4 FINGER TAPPING
0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.5 HAND MOVEMENTS
0: Normal: No problem.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.
2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.
3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS
0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.
2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.
3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.7 TOE TAPPING
0: Normal: No problem.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.
2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.
3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.8 LEG AGILITY
0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.
2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.
3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.9 ARISING FROM CHAIR
0: Normal: No problems. Able to arise quickly without hesitation.
1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.
2: Mild: Pushes self up from arms of chair without difficulty.
3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.
4: Severe: Unable to arise without help.

3.10 GAIT
0: Normal: No problems.
1: Slight: Independent walking with minor gait impairment.
2: Mild: Independent walking but with substantial gait impairment.
3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person.
4: Severe: Cannot walk at all or only with another person's assistance.

3.11 FREEZING OF GAIT
0: Normal: No freezing.
1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.
2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.
3: Moderate: Freezes once during straight walking.
4: Severe: Freezes multiple times during straight walking.

3.12 POSTURAL STABILITY
0: Normal: No problems: Recovers with one or two steps.
1: Slight: 3-5 steps, but subject recovers unaided.
2: Mild: More than 5 steps, but subject recovers unaided.
3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner.
4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.

3.13 POSTURE
0: Normal: No problems.
1: Slight: Not quite erect, but posture could be normal for older person.
2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so.
3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient.
4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.

3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)
0: Normal: No problems.
1: Slight: Slight global slowness and poverty of spontaneous movements.
2: Mild: Mild global slowness and poverty of spontaneous movements.
3: Moderate: Moderate global slowness and poverty of spontaneous movements.
4: Severe: Severe global slowness and poverty of spontaneous movements.

3.15 POSTURAL TREMOR OF THE HANDS
0: Normal: No tremor.
1: Slight: Tremor is present but less than 1 cm in amplitude.
2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.
3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.
4: Severe: Tremor is at least 10 cm in amplitude.

3.16 KINETIC TREMOR OF THE HANDS
0: Normal: No tremor.
1: Slight: Tremor is present but less than 1 cm in amplitude.
2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.
3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.
4: Severe: Tremor is at least 10 cm in amplitude.

3.17 REST TREMOR AMPLITUDE
Extremity ratings
0: Normal: No tremor.
1: Slight.: < 1 cm in maximal amplitude.
2: Mild: > 1 cm but < 3 cm in maximal amplitude.
3: Moderate: 3 - 10 cm in maximal amplitude.
4: Severe: > 10 cm in maximal amplitude.

Lip/Jaw ratings
0: Normal: No tremor.
1: Slight: < 1 cm in maximal amplitude.
2: Mild: > 1 cm but < 2 cm in maximal amplitude.
3: Moderate: > 2 cm but < 3 cm in maximal amplitude.
4: Severe: > 3 cm in maximal amplitude.

3.18 CONSTANCY OF REST TREMOR
0: Normal: No tremor.
1: Slight: Tremor at rest is present < 25% of the entire examination period.
2: Mild: Tremor at rest is present 26-50% of the entire examination period.
3: Moderate: Tremor at rest is present 51-75% of the entire examination period.
4: Severe: Tremor at rest is present > 75% of the entire examination period.

DYSKINESIA IMPACT ON PART III RATINGS
A. Were dyskinesias (chorea or dystonia) present during examination?
No
Yes
B. If yes, did these movements interfere with your ratings?
No
Yes

18.4 Appendix 4: Hoehn and Yahr Scale

0: Asymptomatic.
1: Unilateral involvement only.
2: Bilateral involvement without impairment of balance.
3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
4: Severe disability; still able to walk or stand unassisted.
5: Wheelchair bound or bedridden unless aided.

18.5 Appendix 5: UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria(9)

Step 1. Diagnosis of Parkinsonian Syndrome
- Bradykinesia
- At least one of the following
    - o Muscular rigidity
    - o 4-6 Hz rest tremor
    - o postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease
- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease
Three or more required for diagnosis of definite Parkinson's disease in combination with step one
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more